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THE POLIOMYELITIS EPIDEMIC IN MALTA 1942–3[1]

By H. J. SEDDON, THOMAS AGIUS, H. G. G. BERNSTEIN, and R. E. TUNBRIDGE

Introduction

On June 10, 1940, Italy declared war on Great Britain. At five minutes to seven on the following morning Malta suffered its first air raid, and from that time until late in 1942 the island was bombarded with a remorseless regularity unsurpassed in the history of warfare. The Grand Harbour is surrounded by the most densely populated part of the island, and as would be expected this is where the destruction was greatest. In the words of Professor A. V. Bernard, Chief Government Medical Officer (Annual Report, 1940), 'In the danger areas large numbers of people established themselves in tunnels, basements, crypts of churches, caves, etc., and shelters that had been prepared for temporary occupation during air raids became residential quarters. In the reception areas refugee families had to be accommodated in schools, old churches, corridors of convents and similar places. In some of these places even the most essential sanitary requirements were lacking and in others the conveniences that existed were quite inadequate for the number of people that had come to live there. Overcrowding continually increased as more dwelling houses were demolished or damaged.' Later, although overcrowding persisted, the provision of deep shelters, hewn out of the rock of which the island is composed, relieved the pressure considerably, so that some of the schools, for example, were no longer occupied by refugees. The Maltese islands are among the most densely populated parts of Europe. The area of Malta is 95 square miles, Gozo 27; total 122 square miles. The estimated population of the two islands in 1941 was 271,359. The number of persons per square mile was 2,551 in Malta and 1,087 in Gozo. In addition, increasing numbers of sailors, soldiers, and airmen were landed on these islands, which together are rather smaller than the Isle of Wight.

The aerial bombardment took on a new fury when H.M.S. *Illustrious* limped into the Grand Harbour in January 1941; the Three Cities, lying to the east of the Grand Harbour, were almost completely destroyed. From then until July 1942 'attacks on all parts of the Island continued day after day, right through the night; while on some days alerts persisted without respite very nearly twice round the face of the clock. Other towns and villages were almost completely destroyed and many dwellings in all parts of the island were shattered' (Bernard, 1941). Rommel's advance towards

[1] Received August 28, 1944.

Egypt in June 1942 was almost the undoing of the already precarious supply line on which Malta was dependent. The result was that in the summer and autumn of 1942 the supply of food, which had been steadily diminishing, became dangerously low. A most drastic system of rationing had to be introduced, and the population of the main island no longer had enough to eat; it was not until the turn of the tide in November that the arrival of supplies relieved a situation that had become desperate. It was at this time, in the middle of November, that the poliomyelitis epidemic started.

The present paper is concerned only with the main epidemiological features of the outbreak. The details of diagnosis and treatment will be described elsewhere. It is regrettable that the epidemiological data are incomplete, but the stress of circumstances and the urgent need for dealing with patients prevented us from making the searching inquiries that are called for in any serious attempt to trace the origins and mode of spread of poliomyelitis. One of us (H.J.S.) was not even in Malta until the epidemic was almost over.

The Epidemic

There was a small outbreak of poliomyelitis in Malta in 1902, but the recent epidemic was the first of any magnitude. Only 61 cases were recorded during the period 1921 to 1941 (Table I). The largest number of cases in any one year was nine in 1921. Prior to November no case had been notified for the year 1942. We do not consider that the recorded incidence during the period represents the total incidence, because one of us whilst acting as Chairman of the local Recruiting Board saw about 20 men in the 18 to 23 years age group who were suffering from the effects of anterior poliomyelitis. Furthermore, late cases have been seen not infrequently in the surgical departments of the civilian hospitals, the diagnosis then being made for the first time. This is the usual state of affairs in countries like Malta and England where the disease is predominantly sporadic.

TABLE I

Notified Cases of Acute Anterior Poliomyelitis: Malta, 1921 to 1941

Year	Cases	Deaths	Year	Cases	Deaths
1921	9	—	1932	3	1
1922	—	—	1933	3	1
1923	3	—	1934	2	—
1924	—	—	1935	1	—
1925	6	—	1936	3	—
1926	1	—	1937	6	—
1927	5	1	1938	5	—
1928	3	—	1939	2	—
1929	4	—	1940	—	—
1930	—	—	1941	1	—
1931	4	—			

The first known cases occurred on 15.11.42 in Malta, on 21.11.42 in Gozo, and on 27.11.42 in the services. The epidemic reached its peak (Table II, Fig. 1) in the week beginning December 20 when there were 108 cases, and

by March 1, 1943, the epidemic was over, though a few sporadic cases appeared later. In this epidemic the disease merited its old name of infantile paralysis, since 82 per cent. of the cases occurred in children under five years of age (Table III, Fig. 3). There were three cases among the children of men

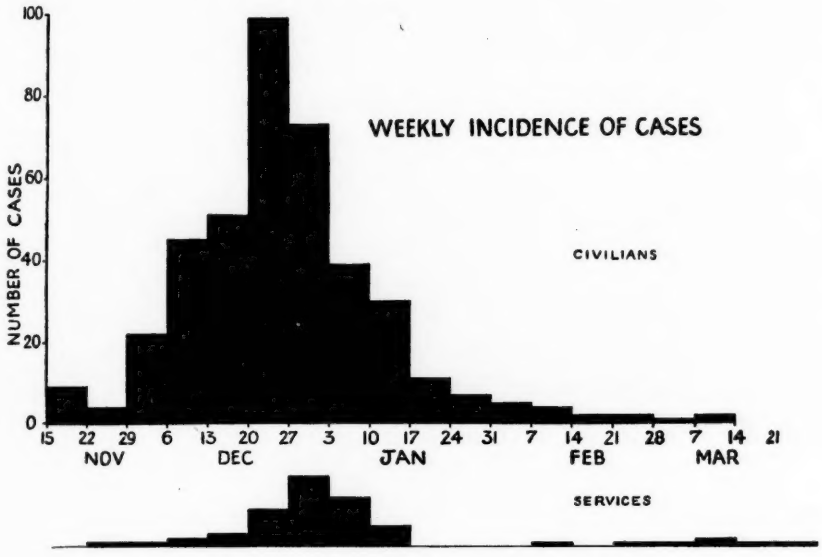

FIG. 1. Weekly incidence of cases, based on dates of onset.

TABLE II

Incidence of Cases

Week beginning	Malta (civilians)	Gozo (civilians)	Malta (services)
1942: November 15	6	3	—
22	3	1	1
29	13	9	1
December 6	40	5	2
13	44	7	3
20	90	9	9
27	71	2	17
1943: January 3	39	—	12
10	29	1	5
17	11	—	—
24	7	—	—
31	5	—	—
February 7	4	—	1
14	2	—	—
21	2	—	1
28	1	—	1
March 7	2	—	2
Date of onset unknown	15	1	1
Late cases (April 2 to June 2)	—	4	1
	384	42	57
	426		57

in the armed forces, which are included among the civilians, since with one possible exception these children were born in Malta. There were 483 cases in all: 426 civilians and 57 in the services. It is to be noted that among the 61 adults, those over 20 years of age, there were only four Maltese. Among the four adult civilians affected, one case was remarkable in that the victim was a patient of 59 years; he died from respiratory paralysis. There were 312 male (255 civilians, 57 men in the services) and 171 female patients.

TABLE III

Age Incidence

Age groups	Civilians		Services
	Both islands	Gozo	
0 to 3 months	8	1	—
4 to 6 months	21	1	—
7 to 9 months	21	3	—
10 to 12 months	19	1	—
Total under 12 months	69	6	—
0 to 1 year	69	6	—
1 to 2 years	114	13	—
2 to 3 years	109	8	—
3 to 4 years	72	7	—
4 to 5 years	33	5	—
Total under 5 years	397	39	—
0 to 5 years	397	39	—
5 to 10 years	23	1	—
10 to 20 years	2	—	—
20 to 30 years	1	—	47
30 to 40 years	1	—	8
40 to 50 years	1	—	2
over 50 years	1	—	—
Total	426	40	57

TABLE IV

Duration of Stay in Malta

One month and under	4
One to six months	7
Seven to twelve months	4
Thirteen to twenty-four months	31
Over two years	11
Shortest period of service	2 weeks
Longest „ „	5¾ years
Average „ „	over twelve months

The service incidence was as follows: Royal Navy 2, Army 27, Royal Air Force 28, and all were from the United Kingdom. No case was observed among the Maltese troops. The latter observation was the more striking since in a number of units Maltese and United Kingdom troops worked together, and many others employed Maltese cooks and labourers. The incidence was proportionately higher among the Royal Air Force than among

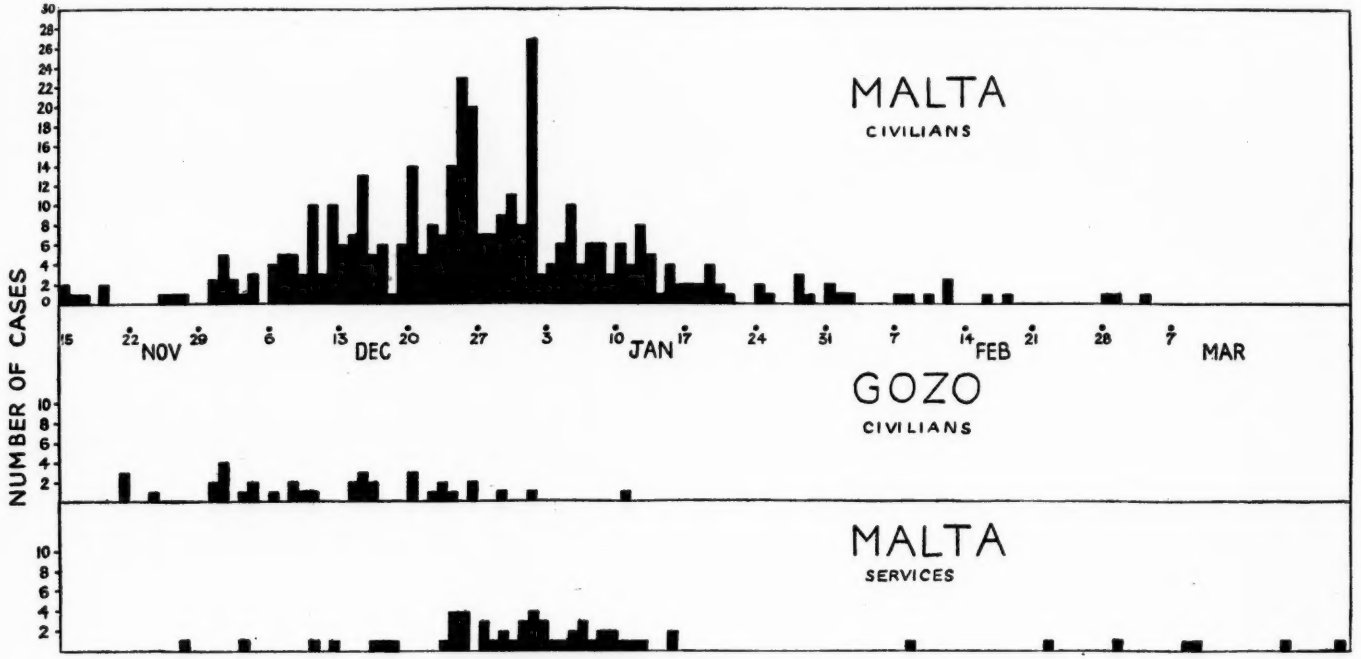

FIG. 2. Daily incidence of cases, based on dates of onset.

the Army personnel, approximately 4 to 1. The duration of service in Malta of the affected men is shown in Table IV; the average was over 12 months. In only four cases was the period one month or less, and as none of the four came to the island before December 1942 they cannot be held responsible for introducing the infection.

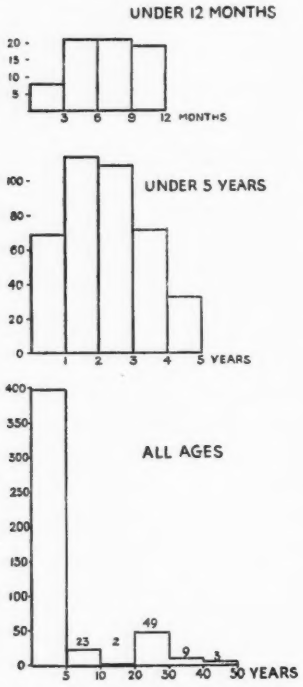

FIG. 3. Age incidence. The 20 to 40 years group is accounted for almost entirely by service cases.

Non-paralytic cases. In any outbreak of poliomyelitis there are usually many cases in which paralysis never develops. Under epidemic conditions the diagnosis is made on the evidence of a suggestive history and the finding of those symptoms and signs which experience has led us to associate with the infection in the prodromal and ingravescent phases. Unless the clinical suspicion is confirmed by positive findings in the cerebrospinal fluid, the diagnosis is only presumptive though reasonably probable. In this epidemic it was not possible to identify non-paralytic cases among the civilians, but in the services a careful watch was kept for suspicious cases, and almost all men complaining of headache and fever were admitted to hospital and their cerebrospinal fluid examined. In spite of this vigilance only two non-paralytic cases were found, but it is reasonable to suppose that a number of persons suffered from the infection without developing paralysis and, as will be shown later, there were histories suggestive of infection in a few contacts.

Incubation period. The civilian case histories throw no clear light on the length of the incubation period, but there are a number of instructive service cases.

(*a*) An orderly at a military hospital did not leave the hospital area during the Christmas period. He was put on night duty in the poliomyelitis ward on the night of December 25/26, 1942. He developed the disease, and the first symptoms were noted on 2.1.43. Interval eight days.

(*b*) A patient with poliomyelitis was admitted on 17.12.42, four days after symptoms appeared. He was seen by an officer on December 16 or 17; this officer developed symptoms of the disease on 28.12.42, and was admitted with poliomyelitis on the 30th. Interval 11 to 12 days.

(*c*) A sailor, living on board one of H.M. ships, developed the disease during the epidemic period, having been ashore at intervals during two weeks. Interval 14 days or less.

(*d*) Another man, who had been in Malta for only three weeks, developed the disease on 16.1.43. Interval three weeks or less.

(*e*) H, who had been in Malta for four months, first showed signs of the disease on 11.12.42, and was admitted to hospital two days later. D, who lived in an adjoining room, developed symptoms on 2.1.43. He had been in Malta for only three weeks; he had had, therefore, 1 to 2 days' opportunity of contact with his neighbour. Interval 20 days.

(*f*) L had been in Malta for two months and D shared his room. L developed symptoms seven days after D was taken ill. Interval over seven days, but not more than 28.

(*g*) Two men working together at Gomerino, but not sleeping in the same room, were taken ill on 1.1.43 and 8.1.43 respectively. Interval seven days.

As the contacts of these cases with Maltese service men and civilians are unknown, the data cannot be rated very highly, though they are of interest. Professor Arthur Ellis has pointed out to us that the daily case-incidence chart, which was worked out from the dates of onset of the disease, shows peaks at intervals of 7 to 10 days (Fig. 2), which may perhaps indicate that some such period (or a multiple of it) elapsed between infection and the development of definite symptoms and signs; the service case histories suggest that 7 to 10 days may not be very wide of the mark.

Mortality rate. Civilians. The rate was low, especially when one takes into account the exclusion of non-paralytic cases.

Mortality rate due to poliomyelitis alone	3·5 %
Mortality rate in cases in which poliomyelitis was an aggravating factor	2·6 %
Total	6·1 %

The children who died from other conditions, though the paralysis may have hastened death, were all under three years; the primary causes of death are much the same as those found at any time in this age group in Malta (Table V).

Service cases. There were 11 fatalities; mortality rate 19·3 per cent. In all but two cases death was due to respiratory paralysis; two late deaths were due to cerebral anoxia.

Epidemiology

Epidemics have a heightened interest when they occur in comparatively isolated communities; and where the origin and mode of spread of the infection are obscure, as in poliomyelitis, study of such outbreaks may yield information of considerable value. There are many reports of epidemics of poliomyelitis in villages, colleges, schools, and orphanages, and a certain number in even more remote communities such as Samoa (Lambert, 1936), the Solomon islands (James, 1938), Madagascar (Fontoynont and Rahari-jaona, 1930), Porto Rico (Garrido Morales, 1930), and Greenland (Hrolv, 1935). Although the conclusions reached by these observers are remarkable chiefly for their diversity, the temporal incidence of the outbreaks shows that the regular seasonal appearance characteristic of the disease in countries in the temperate zones is by no means universal (Epidemiological Reports,

TABLE V

Causes of Death

Case number	Age: Years	Age: Months	Survived for (days)	Cause of death
			CIVILIANS	
			Fatalities directly attributable to Poliomyelitis	
411	—	7	1	Respiratory paralysis
116	—	8	3	
259	1	—	2	Convulsions
238	1	6	1	Respiratory paralysis
493	3	—	1½	
379	3	4	13	
286	3	6	11	
154	4	—	67	
290	5	—	3	
435	5	3	103	
217	5	4	2	
377	7	6	5	
177	7	6	10	
103	42	—	12	
421	59	—	29	
			Total = 15 cases	
			Fatalities in which Poliomyelitis may have been a contributory factor	
384	—	3	51	Marasmus
390	—	4	73	Marasmus
216	—	5	48	Enteritis
412	—	7	70	Marasmus
446	—	10	65	Enteritis
367	1	2	56	Enteritis
213	1	3	66	Tb. peritonitis
281	1	8	70	Lobar pneumonia
423	2	2	70	Acute generalized infection
327	2	6	78	
291	2	6	15	?
			Total = 11 cases	
			SERVICES	
9	22	—	7	Respiratory paralysis
2	23	—	5	
18	23	—	102	Cerebral anoxia
55	23	—	8	Respiratory paralysis
21	24	—	2	
7	25	—	8	
6	26	—	205	Cerebral anoxia
8	29	—	4	Respiratory paralysis
41	29	—	4	
47	31	—	8	
37	43	—	4	
			Total = 11 cases	

Health Section, League of Nations, 1935). In Samoa (Lambert, 1936), just south of the equator, an epidemic occurred during the months February to May, in Porto Rico (Garrido Morales, 1930), April to June, and in Syracuse, New York State (Silverman, 1941), March to April. Hence, although there is no explanation for the unusual time of appearance of the outbreak in

Malta (November to February) such irregularity cannot be regarded as uncommon. The winter months are cool like an English autumn (temperature 50° to 60° F.), with more rain than at any other time of the year (about 100 mm. in December and the same amount in January); and rain may fall on more than half the days in the months of November, December, and January. The weather during the winter months of 1942–3 was not exceptional, except that there were heavy gales of wind and rain shortly before the outbreak. Among United Kingdom service personnel there was an increase in the incidence of common colds during the last two months of 1942.

Overcrowding. Overcrowding of civilians had been serious since the summer of 1940, especially during the months between late 1941 and the autumn of 1942, when intense aerial bombardment drove thousands of people into shelters, and others whose homes had been destroyed to seek refuge with friends in outlying towns and villages. However, the epidemic came at a time when many people had returned to sleeping in houses, though the overcrowding was still considerable. Some idea of living conditions at the time of the epidemic may be gathered from Fig. 4. Two measures of overcrowding were used, the number of persons sleeping in the same room as the patient, and the number sharing a bed with the patient. Yet there were only seven homes in which more than one child was affected, and none in which there were more than two cases. Hence it may be concluded that overcrowding was not an important factor in determining the case morbidity, though it may well have contributed to the dissemination of the causal virus. It is also likely that there must have been a high degree of immunity, as is usually the case in a predominantly urban population (League of Nations, 1935). In the services there was some overcrowding of airmen, but none to speak of among sailors and soldiers.

Malnutrition and under-nutrition. During the summer and autumn of 1942 the daily adult calorie consumption was not more than 1,500 and often as little as 1,100. The children received less. There were, however, three sections of the population whose diet was more liberal.

(*a*) Gozo is more fertile than Malta, and at the time of the epidemic the population density was about one-third of that in the main island. The Gozitans enjoyed their own abundant produce and probably kept well above starvation level.

(*b*) The rations of men in the services worked out at about 2,300 calories, but, although the allowance was more liberal than that for civilians, sailors, soldiers, and airmen alike were subjected to great and unmitigated physical and mental strain, though no more than in the case of many civilian workers. The arduous work of defence had to go on.

(*c*) It is probable that the more affluent classes had reserves of food and it is certain that they patronized the black market, but from the nature of the case it was not possible to know how these people fared, and they cannot therefore be used as controls.

Examination of the incidence of the disease shows that the Gozitans were affected to the extent of 1·7 cases per 1,000, the services 2·5 per 1,000, and

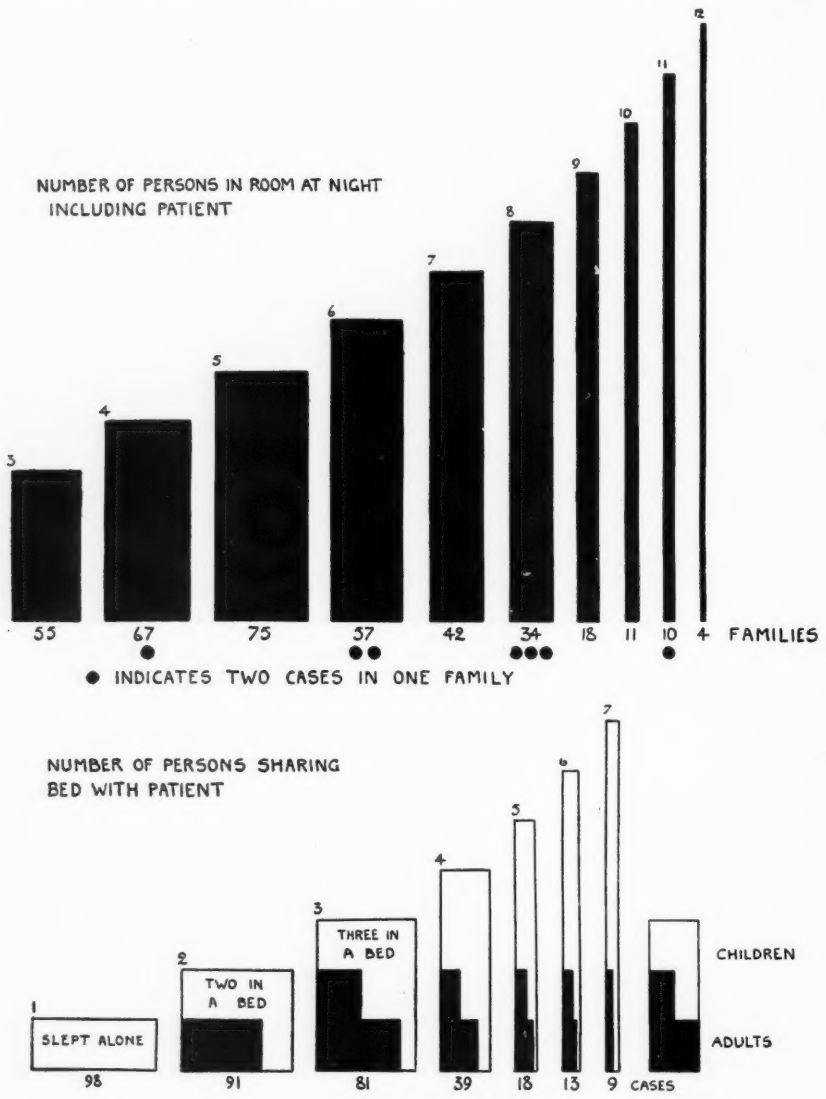

FIG. 4. Overcrowding. In the upper diagram the height of each column shows the number of persons sleeping in one room, the breadth, the number of families in each group. In the lower diagram adults are indicated by black shading; the widths indicate the numbers of families and the heights the proportions of children and adults.

the Maltese civilians 1·64 per 1,000. If diet had any influence on the incidence of the disease it is certainly not revealed by these figures. There

was also a considerable degree of vitamin deficiency, though the only estimate of its extent known to us is that given by Lapira (1943).

	A	B[2]	C
Communal kitchen: week ending 27.11.42	488	77	5·7
Ration: issue period beginning 21.11.42	85	23	0
Bread: about 1·4 lb. a day	0	302	0
	573 i.u.	402 i.u.	5·7 mg.
Recommended allowances (National Research Council)	5,000 i.u.	500 i.u.	75·0 mg.

Some 120 patients with ulcerative stomatitis came under his care during the months of November and December, 1942, which happened to be the peak period of the epidemic, and the only remedy which he found effective was ascorbic acid. The patients came from all parts of Malta and, almost without exception, were in poor health. There were also some disorders very suggestive of hypovitaminosis among service personnel, though their frequency was unknown. Between August and November 1942 there were at least 10 cases in previously fit young men of oedema of the legs accompanied by loss of energy and proneness to fatigue. Examination, including electrocardiography, failed to reveal any other abnormalities, and there was no evidence of peripheral neuritis. Blood-protein estimations were not possible, but there was no deficiency of protein in the service diet at that time. Complete and permanent recovery followed the administration of vitamin B_1. During December 1942 and January 1943 there was an outbreak of glossitis, and this was at a time after the calorie value of the diet had been increased, though the increase was mainly in the carbohydrate intake. Lastly, there was a fairly general deterioration in the power of dark adaptation; as the nights were fairly light this was more noticeable than actual night-blindness.

Age. There was no doubt that among the civilian population youth was a predisposing factor. Among infants from birth to three months the incidence was relatively low (Table III, Fig. 3); this suggests that some kind of immunity had been transmitted from mother to child (Aycock and Cramer, 1930), but if this was so the protection was only passive and therefore of limited duration. The incidence of disease was greater in the fourth to the twelfth month, rose to a peak in the second and third years, was still high during the fourth and fifth years, and then fell rapidly, so that after the tenth year, excluding the services, there were but six cases. The susceptibility of the youngest and next to the youngest children is shown in Fig. 5. It is conceivable that if, as seems likely, the virus had been prevalent for a long time in the island the almost complete immunity of the adolescent and adult population might be the result of exposure to small doses of virus sufficient to confer immunity without producing more than an occasional case of frank paralysis. But many children under five, and some under 10 years, had failed to become immunized, either through lack of exposure or because of

[2] Presumably thiamine.

some intrinsic defect; they therefore fell victims to the disease when distribution of the virus became widespread. If this hypothesis is correct, the immunity in the greater part of the population must have been of a high order, for the disease appeared in almost every town in both islands (Fig. 6).

Social status. In only 14 of the Maltese families affected could their circumstances be described as comfortable. It may be that the children of

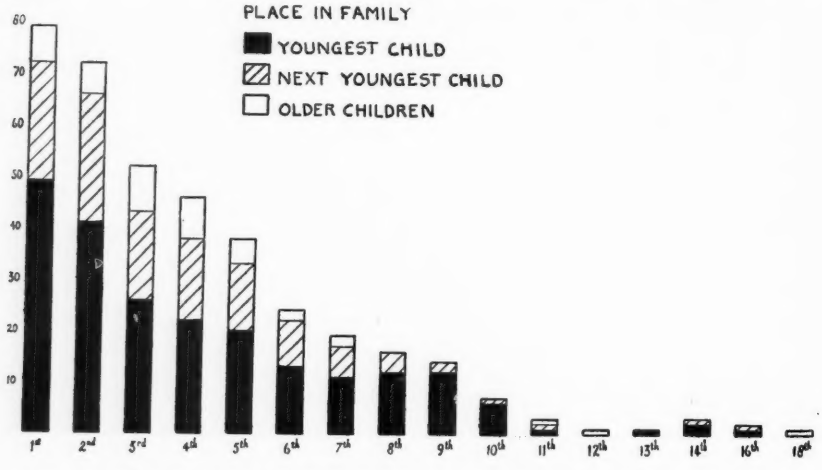

FIG. 5. Place in family of affected children: the number of children who were the 1st, 2nd . . . 18th in the family is shown in each column.

the well-to-do largely escaped because they were kept at home as soon as news of the epidemic became generally known. It has been supposed that a high degree of domestic protection accounts for the comparative frequency of the disease in those children from good families who do by chance come into contact with the infection (cf. influence of overcrowding), and it may be significant that all except five of the service patients came from 'middle-class' families or were earning more than £3. 10*s.* a week before the war. The exceptions were three regular soldiers, and two skilled craftsmen.

Mode of spread. Men in the services did not enjoy the same freedom from infection as the adult Maltese, and 57 of them fell victims to the disease. Without exception they were not natives of the island. Thus it is reasonable to suppose that this minority had come into contact with a virus that was new to them and to which they were susceptible. Yet they came from countries in the temperate zones where poliomyelitis is endemic, and had reached an age at which immunity is generally present. There must have been a high grade of immunity in the majority, since only a small proportion of the total number of men from overseas were affected. It may well be that the unfortunate minority had not acquired immunity to the strain of virus concerned in this epidemic. It is known (Howe and Bodian, 1942, 198) that immunity to one strain of virus may fail to protect against infection with

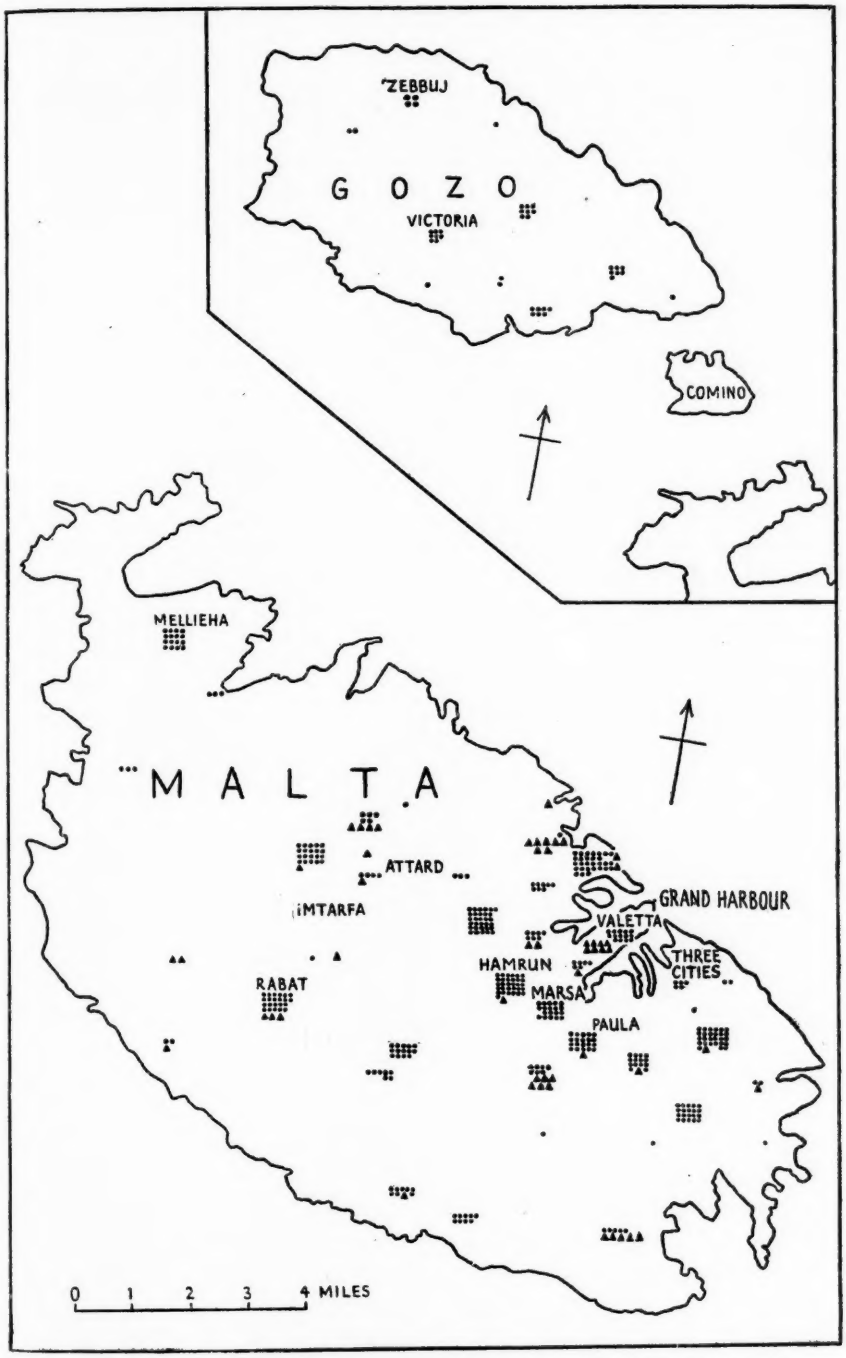

FIG. 6. Geographical distribution of the 450 cases in which the habitat could be determined with certainty.

• civilian case. ▲ service case.

another strain, and this is the explanation usually given for the rare cases of second attacks of the disease. Those who were affected suffered severely; the mortality rate was 19·3 per cent., at least four times as great as that among the civilians, and among the survivors there was a grave residue of disability. Hence we may conclude that the Malta strain or strains of virus did not correspond completely with those found in the United Kingdom.

There was an influx of some 200 airmen during October and November, and it is conceivable that there were carriers among them, since the service cases occurred in men who for the most part had been in the island for a long time. However, the civilian epidemic started two weeks before the outbreak among service personnel, and it was three weeks before an airman was taken ill. Furthermore, the civilian epidemic did not start in places where there were large concentrations of Royal Air Force personnel, and when it did begin, the adult Maltese escaped completely. Thus there is no real evidence that the infection came from without.

There is an interesting parallel between the epidemic and the outbreak of infective hepatitis in Palestine described by Cameron (1943), in which a considerable number of British troops were affected. 'It appears that the disease has been regarded as sporadic rather than epidemic, that young people and especially children are prone to infection, and that new arrivals in the country are more likely to be infected than those born in Palestine. Spirochaetal jaundice has also been encountered, but all were agreed that the sporadic cases were not of this type. The view was advanced by many physicians that a large number of children acquire the disease in a mild form and are immune for life, thus reducing the incidence in the adult native population. With each new immigration of settlers a new non-immune child population is added, and this accounts for epidemics in children during their first two years in the country. So well known is this belief that the disease has been called "German jaundice", since so many immigrants have come from that country. The arrival of British troops represents another immigration, the only difference being in age.'

The incidence of cases in relation to the population of each town (total population and children under four years of age) has been worked out in detail. There are such bewildering and to us inexplicable differences that the tables have not been included. The ratios ranged between 0·2 and 9·8 per 1,000 total population, and between 2 and 50 per cent. of the population of 0 to 4 years of age.

It was not possible to trace any geographical march of the epidemic. The time of appearance of cases in the various towns and within each town was studied; there was no regular connexion so far as we could see between the date of appearance of the disease in one town and its appearance in neighbouring towns, perhaps only a mile or two away. No single service unit had more than three cases, squadrons of the Royal Air Force living together being considered as one unit. Detailed study of the movements of individuals

might have thrown light on the mode of spread, but in the time at our disposal such an elaborate investigation was out of the question; it would have involved taking full accounts of the movements of at least 2,000 persons. However, certain classes of apparent contact infection were examined (Table VI). The civilians are grouped under three headings in decreasing order of intimacy, cases in the same household, cases in adjoining houses, and cases among relatives who visited each other with some frequency. It is by no means clear that in each instance the infection was transmitted as a result of contact between the cases appearing together in Table VI, since in several the onset was on the same day, A. 6, B. 8, B. 9, B. 10, or with only a short interval, A. 1, A. 4, and B. 6. These children may well have developed the disease as a result of almost simultaneous contact with a third (but, to us, unknown) source of infection. On the other hand, the time intervals in B. 5 and C. 3 were so long that personal contact probably had no significance. It is conceivable that droplet spread from older children or adults who were either carriers or suffering from the disease in its non-paralytic form was responsible for the overt infection of the younger members of a family. In 24 apparently unaffected contacts, 23 adults and one child, there was a clear history of coryza at the time when a child in the house was stricken with the disease.

In four service cases (see p. 6) there was presumptive evidence for case-to-case infection. One further case, not included in our series, may have contracted the infection in hospital by means of a carrier. He was admitted to hospital direct from one of H.M. vessels some time before the outbreak of the epidemic. He left hospital in January 1943 and travelled by air. He reported sick within 24 hours of departure and a diagnosis of acute anterior poliomyelitis was made. The patient had had no access to proved cases of the disease. However, no very clear evidence has emerged for or against the spread of the disease by droplet infection; it is desirable, therefore, to consider an alternative mode of spread, one which has attracted increasing attention during recent years.

Excremental spread. There is now no doubt that the poliomyelitis virus can be excreted in the faeces of sufferers from the disease (Kling, Olin, Magnusson, and Gard, 1939; Vignec, Paul, and Trask, 1939; Trask, Paul, and Vignec, 1940). It may even be found in the excreta of those who have shown no definite signs of paralysis, and the virus may continue to be excreted for as long as 123 days after exposure of the subject to infection (Lépine, Sedallian, and Sautter, 1939). Furthermore, the virus is astonishingly hardy. At room temperature it survives in water for at least 114 days (Kling, Levaditi, and Lépine, 1929) and at refrigerator temperature for at least 100 days (Carlson, Ridenour, and McKhann, 1942). It will persist for four to five months in saturated salt solution at 10° to 12° C. (Clark, Schindler, and Roberts, 1930). Kling, Levaditi, and Lépine (1931) inoculated with the virus commercial butter and butter made in the laboratory; in both instances the virus survived for at least 91 days at −2° C. It will also live for 75 days

TABLE VI

Civilians

CONTACTS

A. Brothers and sisters. (14 children)

	Case number and date of onset		Case number	Interval in days
1	159	7. 1.43	158	3
2	329	25.11.42	328	11
3	374	27.12.42	373	18
4	292	24.12.42	293	1
5	438	26.12.42	439	4
6	465	21.11.42	467	0
7	493	8.12.42	180	15

B. House to house. (20 children)

1	153	20.12.42	152	5
2	124	22.12.42	125	5
3	440	1.12.42	324	21
4	450	9.12.42	451	19
5	219	15.11.42	218	45
6	111	13.12.42	115	2
7	132	31.12.42	142	6
8	216	12. 1.43	217	0
9	150	1. 1.43	151	0
10	455	20.12.42	456	0

C. Relatives. (5 children)

1	315	22.12.42	314	6
2	375	10.12.42	379	14
3	379	24.12.42	446	24

or more in faeces stored in a refrigerator; it was found to be active in two specimens that had made a transatlantic crossing lasting 17 days, without any precautions being taken as to temperature (Trask, Paul, and Vignec, 1940). Howe and Bodian (1942, 102) kept infected stools at about 0° C. for more than a year, without finding any diminution in potency of the inoculum. Most important of all, it may be recovered from sewage (Paul, Trask, and Culotta, 1939) even when there are very few overt cases of poliomyelitis in the catchment area (Trask and Paul, 1942).

Reference has already been made (p. 1) to the sanitary conditions prevalent in Malta as a result of the widespread devastation; even in normal times soil contamination is considerable, excreta being surreptitiously employed for the manuring of crops, especially tomatoes. In the summer of 1942 the prospect of famine was so grave and the hope of obtaining fertilizers from outside sources so slender that the Government reluctantly gave permission for the employment of sewage for farming purposes. In a memorandum dated 16.4.43 the Assistant Director of Agriculture stated that 'The large scale use of sewage on the Government Farm and Marsa Sports Ground commenced on or about the 10th July, 1942, although human food crops grown with this sewage were not available until October onwards. From July

onwards farmers in the following areas were given authority to use sewage on crops normally cooked before consumption.

(1) Mellieha
(2) Imtarfa (between Mdina and Imtarfa)
(3) Rabat (between Rabat and Ta Qali aerodrome)
(4) Attard
(5) Marsa (adjoining the civil abattoir)
(6) Addolorata Cemetery (limits of Paula)

} See Fig. 6.

These areas had their supply of sewage cut off on or about November 9th and the only project continued was that on the Government Farm and Marsa Sports Ground. Even there sewage was not used between the end of November 1942 and the middle of February 1943, owing to an adequate amount of rain. Farmers had been using sewage which was overflowing as a result of bomb damage in the areas (2) and (3) above during the month of May and June without any form of Government control.' Thus there were districts extending in a broken line from near the north-west tip of Malta to the Grand Harbour in which sewage was known to be exposed. No like measures had been sanctioned in Gozo, though excrement had long been used for manuring in spite of the vigilance of sanitary inspectors. There was an outbreak of typhoid fever very soon after the use of sewage on the land was begun (Fig. 7); dysentery also became prevalent at about the same time, though no civilian figures are available since the disease is not notifiable in Malta. It is clear that consumption of infected vegetables could not be held responsible for these outbreaks, since the peak was passed before the crops had come to maturity and been gathered. Chlorination of the water supply was adequate, and there are therefore no grounds for believing that these enteric infections were water-borne. The remaining possibility is spread by flies. In normal times flies abound in Malta during the summer and early autumn. In 1942 they were especially prevalent, conditions for breeding being ideal in the devastated areas. Hence it is reasonable to concur with the opinion expressed by the Chief Government Medical Officer that the typhoid epidemic was fly-borne.

Three possible modes of spread, food, water, and flies, must now be considered in relation to the poliomyelitis epidemic.

Spread by food. Crops. There is some evidence (August and Toomey, 1933; League of Nations, 1935) that the time of harvesting and consumption of certain crops and the seasonal incidence of poliomyelitis are more than coincidental, and although Camps (1940) in reporting the Essex epidemic discounted the view that strawberries may have played some part in spreading the disease, he has recently modified his opinion (1943). In Malta the crops were gathered shortly before the outbreak, yet although it is possible that the disease was conveyed to the civilian population by consumption of infected vegetables, it is difficult to see how the British troops could have become infected, since the kitchen technique of the Army and Royal Air Force would almost certainly have closed this possible source of the virus.

Milk. It was conceivable that some kind of food, other than vegetables or

fruit, issued especially to infants and to service personnel, might have been responsible for spreading the virus, and suspicion fell on dried milk. The facts, for which we are indebted to Mr. H. K. Jones, Superintendent of the Cosup Stocks and Stores, are as follows. The distribution of powdered milk to civilians in Malta and Gozo started on August 24, 1942, and the weekly ration for each person was about $2\frac{3}{4}$ oz. of skimmed milk powder. Children under two years of age received a special ration of 12 units of full cream milk powder for the corresponding period. The total quantities in tons distributed during the relevant months were:

	Skimmed milk	Full cream milk
September	$26\frac{1}{4}$	$14\frac{1}{2}$
October	$31\frac{1}{4}$	$14\frac{1}{2}$
November	$33\frac{1}{4}$	$55\frac{1}{4}$
December	$14\frac{1}{4}$	59

The issue to the services began on October 9 at the rate of $\frac{1}{2}$ oz. a day for each man, increased to 1 oz. between December 2 and 9. On December 10 the ration was increased to 2 oz. of tinned milk a day. There was a different scale for hospitals where everyone, including orderlies, received $1\frac{1}{4}$ oz. a day of full cream milk powder during October, November, and December. Some patients on special diets received as much as $4\frac{1}{2}$ oz. a day. No powdered milk was salvaged from ships sunk in the Grand Harbour, and except when a heavy shower of rain fell on an unprotected open-air dump there was no possibility of contamination of the milk powder before issue. The brands of milk distributed came from well-known firms who have supplied enormous quantities for distribution elsewhere. It is clear that although this article of food was consumed chiefly by children (many of the adult Maltese gave their rations to their children) and by men in the services, consumption began well before the epidemic started; it also continued for long after it was over. Unless one assumes that certain particular batches of milk were contaminated during manufacture and that distribution happened to occur in such a way that these batches of milk powder reached almost every part of Malta and Gozo, both fantastic assumptions, it is impossible to make out a case for incriminating the milk supply.

Shell-fish. Although the Maltese eat shell-fish, especially the eggs of the sea-urchin and sea-hedgehog, the main consumption of these foods is earlier in the year, and they are eaten only by adults.

Water. Several objections have been made to the hypothesis that the epidemic was water-borne, in addition to the more general ones made in the League of Nations Bulletin (1935) and by Maxcy (1943). The epidemic affected mainly infants, a fair proportion of those under one year being breast-fed, and not therefore likely to be large consumers of water. However, supplementary feeding was common, and the dried milk was usually made up with unboiled water.

The island of Malta is a mass of limestone, most of it coralline and comparatively porous; at one stratigraphical level there is a formation of

impervious clay, though this has been completely removed by erosion throughout the eastern half of the island. There are few springs and no rivers, and the water supply is derived from numerous deep shafts and galleries. This (rain) water in its downward passage through the rocks has undergone considerable filtration, but it is improbable that the virus of poliomyelitis would be held back. Carlson, Ridenour, and McKhann (1942) found that

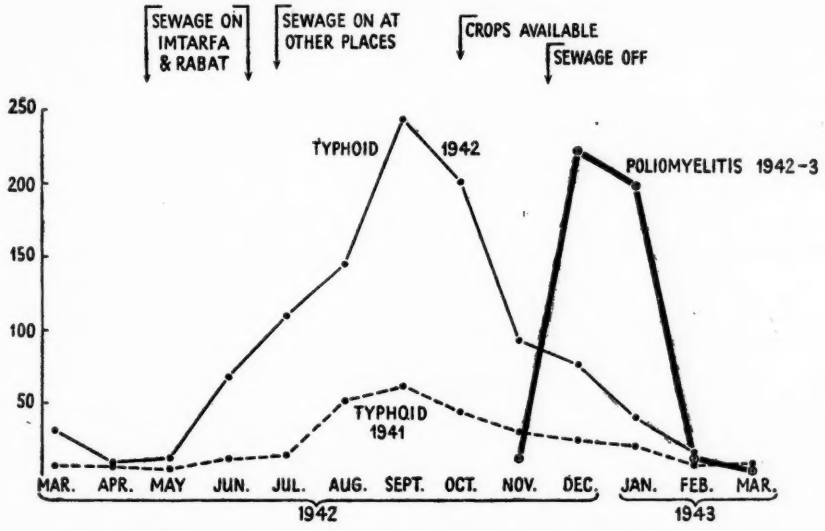

FIG. 7. Relation in time between typhoid and poliomyelitis epidemics.

the virus defied most methods of water purification, such as coagulation and sedimentation, sand filtration, adsorption on activated charcoal, aeration, adjustment of pH, and storage. What is even more disturbing is the failure to destroy the virus of a degree of chlorination adequate to kill organisms of the enteric group (Kempf, Wilson, Pierce, and Soule, 1942).

The water supply of Malta is a complicated affair with many intercommunications. The cases occurring during the first two weeks of the epidemic were scattered over the island, and the 10 towns first affected were severally supplied with water from one or other of at least four and at most six separate sources, the number of the latter depending upon fluctuations in the day-to-day supply. Hence, if the infection was water-borne, it is necessary to postulate simultaneous contamination of four to six water supplies. It must be conceded that the areas in which sewage was used for manuring crops lay near the catchment areas of three sources of supply (Mellieha, Ta Qali, and Wied-il-Kbir), but on the other hand (see p. 16) the use of sewage on the fields began in July and, with the exception of the Government Farm and the Marsa Sports Ground, ceased early in November. From the end of November 1942 until the middle of February 1943 even

the last-named sites were no longer supplied with sewage, owing to the adequacy of the rainfall. Furthermore, Dr. E. L. Sturdee of the Ministry of Health has pointed out to us that Dr. E. B. Bailey, Director of the Geological Survey, stated that the site at Rabat where sewage was used on the fields 'was on or below the clay out-crop that supported the upper water table. Irrigation of this site could not, therefore, affect the galleries or springs draining the latter above the clay. The land irrigated was altogether too far from "anywhere" where the lower water table was exploited to run any risk of affecting that table. The sports ground at Marsa was on the globigerina limestone outcrop which was relatively impermeable and would isolate the sports ground satisfactorily from the tunnels draining the underlying water table in the lower coralline limestone some distance to the south west.' Thus on geological grounds alone contamination of two of the three catchment areas is excluded.

Certain towns had a common water supply; for example, Tarxien, Paula, Zabbar, and Marsascala; yet the case-rate in children under four years was 4·5 per cent. in Tarxien and Paula, and 30·5 per cent. in Zabbar and Marsascala; in Qrendi, Siggiewi, Zurrieq, and Kirkop, all receiving the same supply, the rates were 36, 18, 14, and 0 per cent. respectively. Such irregularities are hardly compatible with a water-borne source of infection. Lastly, the epidemic appeared almost at the same time in Gozo, with its separate water supply. This, of all reasons against incrimination of the water supply, is the strongest.

Flies. Until recently no one had seriously considered flies as vectors of poliomyelitis, although it was shown over 30 years ago that certain species could carry the disease by first biting an experimentally infected monkey and then biting a non-infected animal (Anderson and Frost, 1912; Rosenau and Brues, 1912). In 1941 Paul, Trask, Bishop, and Melnick showed beyond all doubt that flies could carry the virus, and it was probable, in their investigation, that the source was exposed faeces. That flies could pick it up from the sewage effluent from a town where there were cases of poliomyelitis was demonstrated by Toomey, Takacs, and Tischer (1941), while Sabin and Ward (1941) found the virus in collections of flies that had had no known access to excreta, the only apparent source of infection being garbage cans. More detailed work was reported later by Trask and Paul (1943), and Trask, Paul, and Melnick (1943); four of 19 samples of flies collected within epidemic areas during and after the onset of nearby human cases gave positive inoculation tests; and of eight samples collected for the most part during the decline of an epidemic, but within 10 days of the onset of a local case of poliomyelitis, four yielded the virus.

It has already been mentioned that flies were probably responsible for spreading typhoid and dysentery. Did they also play a part in spreading poliomyelitis? The irregular distribution of the cases of the disease suggests this, but it is curious that the epidemic came so much later than is usually the case with poliomyelitis and at a period when flies were not only less

numerous than at any other time of the year, but less numerous than in corresponding periods in preceding years. Furthermore, the rate of development of the epidemic was too rapid. The case is not a strong one.

The portal of entry. Although infection by way of the olfactory bulbs is the 'normal' portal of entry in what used to be the favourite experimental animal, *Macacus rhesus*, evidence has been accumulating slowly but im-

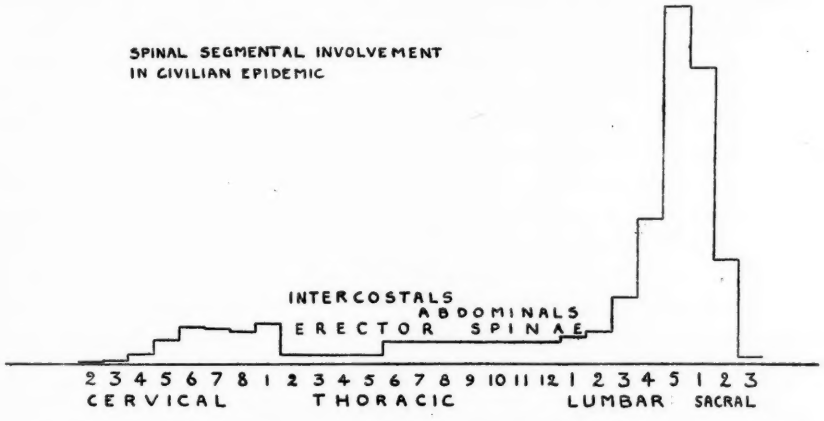

FIG. 8. Spinal segmental involvement, worked out from detailed muscle charts and the root supply (Foerster) of the limb muscles.

pressively in favour of the pharynx and the bowel as the portals of entry in Man, almost to the exclusion of the olfactory route. As long ago as 1913 Flexner, Clark, and Fraser found the virus in the nasopharyngeal washings from healthy carriers, and there have been many tragic cases of bulbar paralysis after tonsillectomy.

Reference has already been made to the demonstration of the virus in intestinal contents. Furthermore, it has been shown that monkeys and apes can be infected by inocula introduced into the intestinal canal (Howe and Bodian, 1942, chap. 6). Toomey (1933) has gone further, and has demonstrated that the virus can travel centrally by way of the abdominal sympathetic system, though Howe and Bodian's (1942) experiments suggest that the abdominal parasympathetic may play an equally important part. The predominance of damage to the lumbosacral segments of the cord is widely recognized, and was a feature of the Malta epidemic (Fig. 8). This has been interpreted, again by Toomey, as evidence in favour of the abdominal portal of entry, though it may be no more than an indication of special susceptibility of the anterior horn cells of the lumbar enlargement. It is important to note that Vignec, Paul, and Trask (1939) found experimentally that the distribution of lesions in the central nervous system bore little relation to the portal of entry, and if this is true in Man the difficulties of assessing the relative importance of the nasal and pharyngeal as opposed to

the abdominal portal of entry become almost insuperable, either by clinical means or post-mortem examination. On the other hand, Leake (1935) found that in 12 cases of paralysis resulting from the injection of attenuated poliomyelitis virus into the upper or lower limb the level of involvement of the cord corresponded very closely with the spinal segmental level of the site of injection. In the Malta epidemic there was no clear correspondence between the initial symptoms and the subsequent distribution of the paralysis. The incidence of abdominal symptoms was about 1 in 4, and the incidence of coryza and other signs of nasopharyngeal invasion about 1 in 5, but it did not follow that a child with abdominal symptoms would develop paralysis referable to the lumbar segments, or on the other hand that upper respiratory symptoms would necessarily precede involvement of the upper limbs or respiratory muscles.

It has been suggested that undue susceptibility to organisms of the enteric group predisposes to poliomyelitic infection gaining entry by the intestinal canal (Toomey, 1931, 1934, 1940). If this is so, then the typhoid epidemic may have paved the way for the epidemic of poliomyelitis, but there have been many previous outbreaks of typhoid in Malta without any corresponding outbreak of poliomyelitis, and, so far as the actual incidence of the two diseases was concerned, there was no correspondence, except in two service cases, in individuals or in age groups. Lastly, although the Maltese troops suffered considerably from both amoebic and bacillary dysentery from the late summer of 1942 to the spring of 1943, there was not a single case of poliomyelitis among them.

The Gozo epidemic. The first cases in Gozo (civilians) appeared on November 21, in Victoria and Zebbuj, six days after the epidemic started in Malta. As will be seen from Table III the age distribution was much the same as in the main island. A holding company of Maltese troops was stationed in Gozo together with some 10 to 15 British troops and about 20 airmen. Immediately before and at the time of the outbreak of the epidemic limited leave to Gozo was granted to men serving on the main island. It is probable that at any one time about 20 men were staying there for their five-day periods of leave. One of the early Army cases was admitted to hospital from Gozo, but it is reasonably certain that the disease had already affected him before he left Malta. There were no other contacts traceable to Gozo.

'All the (civilian) cases in Gozo except one were among inhabitants of that island. This one exception was an evacuee from Sliema, but both patient and parents had been living in Gozo for several months before the epidemic. As far as can be ascertained the first cases in Malta and those in Gozo were in no way related. From September 1942 there had been a ferry service twice a week, on Tuesday and Thursday, but other means of transport were available almost daily between the Grand Harbour and Gozo.' (Information supplied by Dr. C. Coleiro and Dr. A. E. Bartolo.)

Epidemiologically, the outbreak in Gozo is crucial, for the almost simultaneous appearance of poliomyelitis in two neighbouring islands greatly

reduces the scope of inquiry into possible modes of spread. It is, therefore, all the more lamentable that greater advantage could not be taken of the remarkable circumstances of this epidemic; the pressure of events was too great, and there were no facilities whatever for the isolation and identification of viruses. It was difficult to see how the exposure of infected sewage could have been responsible for simultaneous outbreaks through contamination of two entirely separate water supplies. Contamination of crops was a possibility, but reasons have already been adduced why this was unlikely in Malta as apart from Gozo. An article of food distributed in Malta and Gozo alike would naturally fall under suspicion, but the only common factor of possible significance, dried milk, has already been exonerated. If flies carried the disease (there were unusually few about at the time) by crossing the channel between the two islands, then one would have expected the first cases to appear in those towns nearest the main island. Actually, the reverse happened. One is left, therefore, with the conclusion that the disease was taken from Malta by one or more carriers, and it should not have been impossible in such a relatively small and isolated community to track down the offenders. This, alas, could not be done.

Epidemiological Conclusions

Though it is impossible to say how the epidemic arose, the available evidence suggests firstly that the causal strain of virus differed slightly from the usual endemic Maltese strain, and still more so from the usual endemic British strain, and secondly, that infection was spread mainly by nasopharyngeal droplets and droplet nuclei.

The causal strain may have arisen in Malta itself as a variant of the normal endemic strain, or it may have been introduced from outside. It cannot have differed greatly from the normal strain, since its pathogenicity was confined to the more susceptible age groups of the indigenous population, who had presumably not had time or opportunity to become completely protected by the normal process of latent infection. On the other hand, judging from the high incidence and severity of the disease in service men, it must have differed considerably from the strain usually endemic in the British Isles.

That infection was predominantly of the respiratory type is indicated by the general form of the epidemic wave, by the occurrence of cases in all parts of Malta within a very short space of time, and by the almost simultaneous appearance of the disease in Malta and Gozo. The analogy with cerebrospinal fever is very strong. Though infection probably gained access to the nasopharynx by droplets or air-borne droplet nuclei, there is no evidence to show whether the virus reached the central nervous system by the olfactory tract, the lymphatic tissue at the back of the nose and throat, or through some lower portion of the alimentary tract.

Just as in cerebrospinal fever predisposing factors are often present, so it is not impossible that overcrowding, physical and nervous fatigue, and an inadequate dietary contributed to the genesis of the Malta epidemic of poliomyelitis.

Summary

1. During the period November 1942 to February 1943 there was an epidemic of anterior poliomyelitis in the islands of Malta and Gozo. There were 483 cases in all, 426 civilians and 57 men in the services.

2. The incidence fell most heavily on Maltese children under five years of age (82 per cent.); 61 persons over the age of 20 years were affected, and of these only four were Maltese, the remainder, the service cases, being from the United Kingdom.

3. The mortality rate was high in the services (19·3 per cent.) and low among the civilians (3·5 per cent. +), the chief cause of death being respiratory paralysis.

4. That the virus was an indigenous strain was suggested by the following facts:

(*a*) Poliomyelitis has been endemic in Malta for many years, though the annual number of notifications has always been small, and there has never before been an outbreak that could be described as an epidemic.

(*b*) The disease affected civilians first.

(*c*) There was no evidence that the virus had been brought in by men in the services.

(*d*) The adult Maltese were almost completely unaffected, and there were no cases among Maltese soldiers.

(*e*) Although all service personnel, apart from the Maltese, came from the United Kingdom where poliomyelitis is endemic, they were severely affected; the case incidence was 2·5 per 1,000, the mortality rate much higher than that of the native children, and the residual disability among the survivors considerable.

5. There were several unusual circumstances:

(*a*) Great overcrowding, which seemed to play little part in promoting spread of the disease.

(*b*) Lack of food and vitamins, which also appeared irrelevant.

(*c*) The use of sewage in certain parts of Malta for manuring of crops. If it could be assumed that the excreta of a considerable number of persons harboured the virus, then the disease might have been spread by contamination of the water supply or of crops. Such evidence as is available suggests that the water was not contaminated, and it is unlikely that the crops were. It is tolerably certain that the disease was not spread by flies.

(*d*) Dried milk was distributed to both islands, especially to children and to men in the services. It was, however, impossible to trace any connexion between the distribution of this article of food and the geographical incidence of cases of poliomyelitis.

It is a pleasure to record our indebtedness to those without whose help this work could not have been done. Not all can be mentioned by name, since the list is a long one, and we must content ourselves by thanking those most directly concerned: H.E. the Governor, Field-Marshal Viscount Gort, H.H. the Lieutenant-Governor, Mr. D. C. Campbell, Major-General L. T. Poole, Director of Pathology, Army Medical Service, Brigadier W. K. Morrison, D.D.M.S., Malta, the Chief Government Medical Officer, Professor A. E. Bernard, Professor J. E. Debono, and the resident staff at St. Luke's Hospital. As amateurs in epidemiology we owe much to Professor G. S. Wilson who has guided us in the analysis of data and whose criticisms of the paper itself have been invaluable. We are also indebted to Dr. E. L. Sturdee, Dr. E. B. Bailey, and Miss Josephine Ogston.

This paper contains material from a report made by H. J. S. to the Secretary of State for the Colonies, and from a paper read by R. E. T. at the Medical Conference in Cairo, April 1943.

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ADDENDUM

Since this paper was completed a further report has been received from Dr. A. E. Bartolo which contains an account of 12 other fatalities among the children with poliomyelitis, all except one having occurred at least four months after the onset of the disease. The cause of death is known in each case, and in only one could the fatal issue have been connected with the paralysis. In this case, a child of 23 months who had suffered from poliomyelitis since the age of five months, with involvement of the respiratory muscles, died 18 months later as a result of respiratory infection.

The mortality rate due to poliomyelitis (3·5 per cent.) given on p. 7 should, therefore, be increased by 0·2 per cent.; the arguments based on this comparatively low rate are not invalidated.

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GENETIC LINKAGE IN MAN, WITH PARTICULAR REFERENCE TO THE USEFULNESS OF VERY SMALL BODIES OF DATA[1]

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Introduction

The word linkage as used in genetics is a particularly unfortunate invention in biological terminology. Anyone not entirely familiar with the subject is liable to suppose from the common meaning of the word that, if two inherited traits are linked, they tend when observed simultaneously to stick together in hereditary transmission. What actually happens is quite different. In genetics two gene pairs are said to be linked when they are situated upon the same chromosome pair. Instead of being distributed at random, as is found in the absence of linkage, the linked genes producing the traits tend either to stick together unduly often, or, just as frequently, tend to separate unduly often. The older terms coupling and repulsion give a far better idea of what occurs.

In a recent paper in this journal Penfold and Lipscomb (1943) presented observations made possible by an unusual opportunity—the simultaneous occurrence in the same family group of the two rare dominant traits, elliptocytosis and multiple telangiectasia. Sharing this commonest of genetic misconceptions they are led to state that 'The genetic linkage of two or more characters indicates that the genes controlling them exist upon the same chromosome. It follows that except in the rare cases where "crossing over" occurs the two characters will always be found together. In fact this almost invariable association of two characters is the chief clue indicating their linkage.' The misconception immediately becomes evident if for their words 'same chromosome' there is substituted the correct expression 'same chromosome pair'. If the genes are indeed situated on the same chromosome and if linkage is close, the effect will be as they describe, but just as frequently the genes will be situated upon opposite members of the pair. The two characters will then always separate except when crossing-over occurs. Penfold and Lipscomb follow the passage quoted above with the opinion, which would doubtless be equally widely shared, that 'The association of anomalies in our own cases may well be fortuitous since both are inherited as Mendelian dominants; in any event no valid conclusion can be drawn from such small numbers'. This is entirely mistaken. If two rare dominant traits can be

[1] Received October 5, 1944.

observed simultaneously, a family group composed of a mere handful of persons may be sufficient to decide beyond reasonable doubt whether linkage is present or not, or, to be more precise, decide the question which alone can usually be investigated—whether there exists close or moderate genetic linkage. It is true that Penfold and Lipscomb's pedigree is a very small one, yet it will be shown that it is quite sufficient to rule out close linkage.

It is, therefore, the main purpose of the present paper to stress the importance of recording any data on the simultaneous occurrence of two inherited conditions. As has just been said, where two rare dominants are concerned a single small pedigree may provide conclusive evidence. The observer is then in the position of being able to make a solid contribution to the task of mapping the human chromosomes, and, of course, if the opportunity is missed it may not recur for centuries.

The Consequences of Genetic Linkage

It may be helpful to illustrate briefly the consequences of genetic linkage by referring to the simplest case, that of two traits determined by rare dominant genes. A dominant gene produces its effect when only one is present, the other chromosome of the pair concerned bearing the corresponding normal gene. Suppose that elliptocytosis and multiple telangiectasia are not linked, then a person with both anomalies will carry upon one chromosome of a particular pair the gene E for elliptocytosis and on the other member of that pair the corresponding normal gene e. On another chromosome pair will be situated the gene T for telangiectasia and the alternative normal gene t. The two chromosome pairs may be represented thus: (E)(e), {T}{t}. When the reduction division occurs prior to the formation of the gametes, the members of each chromosome pair separate, so that each ovum or spermatozoon contains one chromosome only from each of the 24 pairs found in the human somatic cell. In the present instance a gamete may contain E or e and T or t. Thus four sorts of gametes will be formed in equal proportions: (E){T}, (E){t}, (e){T}, (e){t}. The normal partner of the person with both conditions will contribute only the normal genes, hence it is evident that persons with both these traits married to normal persons will, on the average, produce four kinds of offspring in equal proportions, those with elliptocytosis and telangiectasia, those with elliptocytosis only, those with telangiectasia only, and those with neither condition. If, however, the genes are linked, only one chromosome pair is concerned. There are two possibilities. If both dominant genes are on the same chromosome, the pair may be represented thus: (E, T)(e, t). If crossing-over does not occur only two kinds of gametes can be produced, (E, T) and (e, t). There will be two kinds of offspring only, those with both conditions, and those with neither. On the other hand, the dominant genes may be situated upon opposite members of the pair, thus: (E, t)(e, T). The gametes can only be (E, t) or (e, T). The offspring will show either elliptocytosis or telangiec-

tasia; none will display both and none will be normal. If, therefore, the genes are linked so closely that crossing-over is not observed, it will be found that some persons displaying both traits have offspring displaying both or neither, but not one alone, while others have offspring displaying either one or the other, but not both or neither.

But crossing-over, that is the interchange of segments between chromosomes of a pair, does occur. Should the break take place between the loci of the two genes, gametes of the other kind will be formed. Thus a person (E, T) (e, t) will ordinarily form gametes (E, T) and (e, t), but when crossing-over takes place between the loci the alternative cross-over gametes (E, t) and (e, T) will be formed instead. Similarly, the person who is (E, t) (e, T) will ordinarily form gametes (E, t) and (e, T), but when crossing-over occurs between the loci the cross-over gametes (E, T) and (e, t) will be formed instead. The frequency of crossing-over depends upon the distance apart of the loci of the genes. If they are close together it will seldom occur, if they are far apart it will occur often. Let us suppose that in the present example the frequency of crossing-over is 10 per cent. Then a person with both dominant genes on one chromosome will produce offspring in the following proportions:

Elliptocytosis and telangiectasia	40 %	Non-cross-overs
Neither condition	40 %	
Elliptocytosis only	5 %	Cross-overs
Telangiectasia only	5 %	

If the two dominant genes are borne on opposite chromosomes, these proportions will be reversed. Therefore some persons with both conditions will give offspring 90 per cent. of whom have both or neither, 10 per cent. having one or the other. Other persons will give 90 per cent. with one or the other and 10 per cent. with both or neither. If the genes are very far apart, crossing-over may occur so often that the proportion of cross-overs may approach that of non-cross-overs. The ratios then approach the proportions 1 : 1 : 1 : 1, that is, the proportions found when the genes are situated on different chromosome pairs and there is no genetic linkage at all. In laboratory experiments the true facts are revealed when both genes are found to be linked to a third situated between them. We cannot hope for this in man at the present time, so what can be investigated in practice is not whether linkage exists at all, but whether there is linkage sufficiently close to give only a small or moderate amount of crossing-over.

An Examination of Penfold and Lipscomb's Pedigree

The relevant portion of the pedigree is reproduced in the Figure.

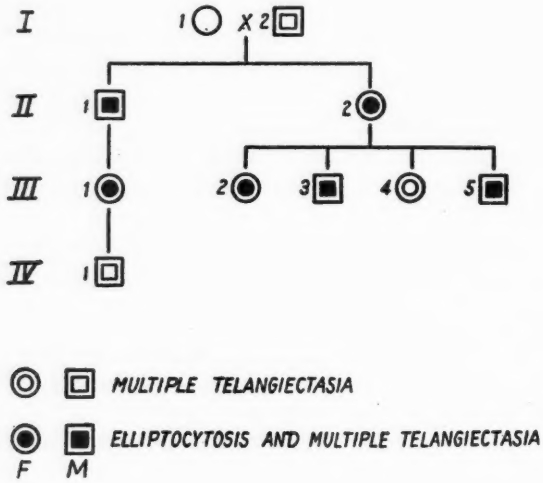
II 2, III 1, III 2, III 3, and III 5 were all examined and found to have both conditions.

IV 1, also examined, had telangiectasia but not elliptocytosis.

III 4 on examination showed no evidence of either anomaly. A son, however, had telangiectasia. This is the phenomenon of 'skipping a generation',

which is not unusual with dominant traits. A person possesses and transmits the gene, but himself displays no outward sign of the condition. It is known that this happens not infrequently in multiple telangiectasia, so it can safely be assumed that III 4 did in fact carry the gene, as indicated in the Figure. The son is not shown, as he furnishes no evidence regarding linkage.

I 1, I 2, and II 1 were dead at the time of the investigation, though there is presumptive evidence that I 2 and II 1 suffered from telangiectasia. In



view of the transmission of elliptocytosis in both lines of the pedigree it can further be deduced that II 1 suffered from elliptocytosis also. There is no means of telling whether it was I 1 or I 2 who bore the gene for elliptocytosis.[2]

One further possibility must be considered. Does elliptocytosis sometimes skip a generation? If so, is it not possible that III 4 or IV 1 might carry the gene, although it is not manifested? The literature provides an answer. In the most considerable group of families, that reported by Wyandt, Bancroft, and Winship (1941), whenever both parents of affected persons were examined, one or the other proved to be similarly affected. This provides no fewer than 63 instances of uncomplicated transmission with no example of the skipping of a generation. In their review of the literature these authors could discover only one example of an affected person with two normal parents. This case was reported by Bernhardt (1928). An affected child had normal parents and siblings and was apparently a sporadic case, possibly due to mutation. I have not found any other example. We can be confident, therefore, that for elliptocytosis to skip a generation is exceedingly rare.

We can now calculate the odds against the hypothesis that elliptocytosis

[2] The chance of mutation has not been considered in the calculations; it is exceedingly unlikely to affect more than one individual in, say, 80,000.

and multiple telangiectasia are linked with a cross-over value of 10 per cent. or less. A summary of the argument is presented in the Table. Either I 1 or I 2 may have carried the gene for elliptocytosis, the chance of either possibility being one-half. Thus the chance that it was I 1 who carried the gene is 0·5. If, on the other hand, it was I 2 who carried the gene for elliptocytosis, he may have carried it on the same chromosome as the gene for telangiectasia or upon the opposite one, the chances again being equal. Hence the chance of each of these two possibilities is 0·25.

Examining the three possibilities in turn:

1. I 1 may have carried the gene for elliptocytosis (chance 0·5). II 1 and II 2 themselves provide no evidence on linkage, but on this assumption they must carry the two genes on opposite chromosomes, received respectively from the two parents. In the absence of crossing-over their children would display either one trait or the other, but not neither or both. Hence III 4 is a non-cross-over, and III 1, III 2, III 3, and III 5 are all cross-overs. III 1 must now carry both genes on the same chromosome, and so her son, IV 1, who has telangiectasia only, is also a cross-over. On this assumption, therefore, the pedigree shows one non-cross-over and five cross-overs. When the percentage of crossing-over is our assumed figure of 10 per cent. or less this is a very unlikely result. The actual chance of getting five or more cross-overs out of six is only 0·000,055, less than 1 in 10,000. Combining this with the chance of the basic assumption itself, that is 0·5, the combined chance is 0·000,028.

TABLE

Hypothesis to be tested: That the Genes for Elliptocytosis and Multiple Telangiectasia are linked with a Cross-over Value of 10 per cent. or less

Possibilities in Generation I	Probability	Non-cross-overs	Cross-overs	Probability of observed or greater number of cross-overs	Combined probability
I 1 had elliptocytosis	0·5	1 (III 4)	5 (III 1, 2, 3, 5, IV 1)	0·000,055	0·000,028
I 2 had both genes in coupling	0·25	6 (II 1, 2, III 1, 2, 3, 5)	2 (III 4, IV 1)	0·186,895	0·046,724
I 2 had both genes in repulsion	0·25	4 (III 1, 2, 3, 5)	4 (II 1, 2, III 4, IV 1)	0·005,025	0·001,256
				Total combined probability =	0·048,008

2. I 2 may have carried the gene for elliptocytosis on the same chromosome as the gene for telangiectasia (chance 0·25). On this assumption II 1 and II 2 both received the chromosome bearing both genes, that is, they are non-cross-overs. Similarly, III 1, III 2, III 3, and III 5 are non-cross-overs. III 4 and IV 1, who display one trait only, are cross-overs. The chance of getting two or more cross-overs out of eight when the cross-over value is 10 per cent. or less is 0·186,895. The combined chance is therefore

$$0{\cdot}25 \times 0{\cdot}186{,}895 = 0{\cdot}046{,}724.$$

3. I 2 may have carried the gene for elliptocytosis on the opposite chromosome to that bearing the gene for telangiectasia (chance 0·25). On this assumption II 1 and II 2 are both cross-overs, the genes having come together in the one chromosome received from their father. The genes are now in the same chromosome, hence III 1, III 2, III 3, and III 5 are non-cross-overs; III 4 is a cross-over; similarly IV 1 is a cross-over. The chance of getting four cross-overs or more out of eight when the cross-over value is 10 per cent. or less is 0·005,025, and the combined chance is 0·001,256.

Adding together these three probabilities the total probability is:

$$0{\cdot}000{,}028 + 0{\cdot}046{,}724 + 0{\cdot}001{,}256 = 0{\cdot}048{,}008.$$

Therefore the odds are 20 to 1 against the hypothesis that the genes are situated so closely upon the same chromosome pair that the cross-over value is 10 per cent. or less. The odds against the hypothesis of a cross-over value of five per cent. or less are 68 to 1. It will be seen, therefore, that small though this pedigree is, and in spite of the uncertainty respecting the first generation, it provides good evidence against linkage close enough to correspond to a cross-over value of 10 per cent. or less, and strong evidence against linkage close enough to correspond to a cross-over value of five per cent. or less.

It will be further appreciated that had a few additional particulars been available, and had there been a few more individuals in the family group, good evidence might have been provided as to the existence of much looser linkage. Those who are fortunate enough to observe two rare dominants simultaneously may quite frequently find themselves able to settle once and for all whether the genes are or are not closely or moderately linked, and this, it may be, with only a small family group available for study.

Summary

1. The term genetic linkage frequently proves misleading. It is often supposed that when two genes are linked they tend to stick together in hereditary transmission. What is actually observed is that, instead of the random distribution seen when the genes are situated on different chromosome pairs, they either tend to stick together unduly often, or, just as frequently, tend to separate unduly often.

2. The consequences of genetic linkage are explained for the case of two rare dominant traits.

3. An examination is made of a pedigree recently recorded by Penfold and Lipscomb, in which elliptocytosis and multiple telangiectasia occurred together in the same family group. The pedigree is a very small one, but it nevertheless provides strong evidence against very close linkage (a cross-over value of five per cent. or less) and good evidence against somewhat looser linkage (a cross-over value of 10 per cent. or less).

4. Observers who encounter the simultaneous occurrence of two inherited conditions in the same family group should on no account omit to place on

record as full a description as possible. It may easily happen that a single small pedigree may be decisive in regard to whether or not there is close or moderate linkage between the genes, thus making possible a solid contribution to the task of mapping the human chromosomes, and, if the chance is missed, so rare an opportunity may not recur for centuries.

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616.36–008.5 : 615.739.116.

THE TREATMENT OF POST-ARSPHENAMINE JAUNDICE WITH SULPHUR-CONTAINING AMINO-ACIDS[1]

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Introduction

Jaundice in the course of or after the administration of organic arsenicals for the treatment of syphilis is a subject which has recently received much attention owing to a very great increase during the war years. The reasons for the increase in incidence are unknown, but an examination of the literature, which indicated that a dietary deficiency might be a predisposing factor, led early in 1943 to an investigation of the value of the administration of sulphur-containing amino-acids in the treatment of this condition. It will be well to review the salient points in the evidence relating to the pathogenesis of the condition and briefly to summarize the theoretical considerations on which the present investigation rests.

Aetiology. In the past there have been three main theories as to causation.

1. Active syphilitic infection is a well recognized cause of liver damage, and Milian (1920) has supported the view that it is the cause of post-arsphenamine jaundice, in fact that hepatitis results from progression of syphilis in spite of treatment, or through under-treatment. It is clear from the evidence presented in the Medical Research Council Special Report No. 66 (1922) that this can only occasionally be regarded as the direct causative factor.

2. The second theory is that jaundice is due to an intercurrent infectious disease of the nature of or similar to infective hepatitis in patients whose susceptibility is possibly increased by the added toxic effects of syphilis and arsenic. In 1920 Stokes, Ruedemann, and Lemon presented a detailed account of 70 cases of jaundice in patients receiving anti-syphilitic treatment

[1] Received October 24, 1944.

at the Mayo Clinic. Only six of these cases occurred during the first two of the four years covered by the study; the remaining 64 occurred between August 1918 and July 1920. It was concluded from this study that while several distinct types of jaundice were probably included in the series, the great majority of cases were not ascribable directly to the effects either of syphilis or of the anti-syphilitic treatment. The symptomatology and seasonal incidence of the cases led, in fact, to the view that the exciting cause was probably an infective agent, although the authors did not exclude the possibility that the administration of arsphenamine may have been a predisposing cause. In 1922 the Salvarsan Committee of the Medical Research Council (Special Report No. 66) concluded that it is 'probable that many of the ill effects of salvarsan may be attributed directly to its arsenical content; and that others again, in particular the effects on the liver, and possibly those on the bone marrow, are due to the chemical nature of the whole compound . . . with the possibility that this type of poisonous action is dependent for its occurrence on the presence of adjuvant circumstances, of a nature as yet unknown'.

With a view to obtaining evidence in favour of the hypothesis that the administration of an arsenical compound might so alter hepatic function as to predispose the organism to the development of intercurrent infections, Findlay, Dunlop, and Brown (1931) reported some experiments consistent with the idea that the toxic action of neoarsphenamine could be increased by the additional injection of a feebly pathogenic micro-organism (a suspension of *B. coli* in saline). Quite recently, the possibility that infection may be transmitted from patient to patient by means of syringes imperfectly sterilized between injections has been suggested by MacCallum (1943) and others. Bigger (1943) showed that the technique employed in many clinics for venereal diseases cannot be relied upon to prevent the transference of an infective agent. The recent work of Salaman, King, Williams, and Nicol (1944), who showed that the incidence of post-arsphenamine jaundice could be greatly reduced by careful attention to technique in the preparation of needles, syringes, and drugs, gives strong support to this view.

3. It is clear that although infection has long been regarded as a probable factor in the aetiology of many cases of post-arsphenamine jaundice, the arsenicals themselves have never been exonerated, at least as predisposing factors. It has been shown repeatedly by a number of workers (Foulerton, 1920, 1921; Hooper, Kolls, and Wright, 1921; Kolmer and Lucke, 1921; Messinger and Hawkins, 1940) that the administration of a wide range of different arsenical compounds (including arsenious oxide, diphenylchlorarsine, arsphenamine, and neoarsphenamine) to experimental animals can produce damage and necrosis of the liver cells in the absence of any coincident spirochaetal or other infection. In man, on the other hand, certain difficulties arise in accepting a purely chemical basis for the pathogenesis of the condition. First, the long interval that frequently elapses between the end of arsenical treatment and the onset of signs and symptoms of liver

dysfunction, and, secondly, the fact that outbreaks of 'post-arsphenamine' jaundice have in the past tended to be localized in time and space, again suggesting the inclusion of some infective agent in the process. Thirdly, many patients have been treated with arsenicals throughout the course of their attacks of jaundice without ill effects; and finally, almost all patients are able to take arsenic after recovery without evidence of recurrent liver damage.

Arsenic and thiol groups. In so far as one possible line of attack is to attempt to prevent or undo any toxic effect that the arsenical may have exerted on the liver it is desirable briefly to review the established facts concerning the nature of the toxic action of arsenic on living cells. Arsenic has often been described as a 'general protoplasmic poison'. Recent work, however, has made it abundantly clear that it is, in fact, highly specific in its biochemical actions, at least so far as its effects in low concentrations on the enzyme systems of living cells are concerned. Onaka (1910) first showed that the respiration of animal tissues is inhibited by the presence of small concentrations of arsenite. This work was confirmed and extended to therapeutic compounds of arsenic by Dresel (1926, 1928), Szent-Györgyi (1930), Voegtlin, Rosenthal, and Johnson (1931), Krebs (1933), and Crasnaru and Gavrilescu (1935). More recently it has been shown by a number of workers that it is only at certain specific points in the chain of enzymatic reactions responsible for the respiratory processes of cells that arsenical compounds exert their toxic effects. Present evidence (Peters, 1937) leads us to believe that the pyruvate oxidase system, an essential component of the cellular mechanism for the metabolism of carbohydrates, is prominent among the arsenic-sensitive enzymes.

In the hope of arriving at a rational treatment of arsenical intoxication, however, it is necessary to go farther and consider the facts and views regarding the particular chemical grouping with which arsenic combines under physiological conditions. As early as 1909 Ehrlich had suggested that the 'chemoreceptors' for arsenic in the tissues might be hydroxyl or thiol groups, and in 1923 reaction with essential thiol groups in the cells was again put forward by Voegtlin, Dyer, and Leonard as the underlying mechanism of its toxic action. In support of this view these workers stated that the trypanocidal action of 3-amino-4-hydroxyphenylarsenious oxide could be abolished by the addition to the trypanosome suspension of cysteine, reduced glutathione, or other simple thiol. In 1928 Walker reported experiments which had been done in association with one of us (R.A.P.) some years previously and at the same time as Voegtlin, Dyer, and Leonard (1923), in which similar conclusions were reached by a different route. Later Voegtlin, Dyer, and Leonard (1925) showed that the toxic action of 'arsenoxide' in rats could be diminished or prevented by the intravenous injection of glutathione immediately before the administration of the arsenical. More recently this work has been extended by Eagle (1939) who has shown that glutathione, and to a lesser extent cysteine, is also capable of abolishing the

anti-spirochaetal action of 'arsenoxide' *in vivo*. It must be pointed out, however, that the protection afforded by these simple thiols was only partial; a large excess of the thiol was required to protect, while reversal of the effects of the arsenical has been even more difficult to achieve. Thus Schmitt and Skow (1935) studied the ability of certain simple thiols to protect or reverse the toxic action of arsenite on the medullated nerves of frogs; they found that while cysteine and reduced glutathione delayed the extinction of the nerve action potential produced by arsenite, in no case were they able to prevent the eventual extinction, regardless of the ratio SH : As. Nor was it possible by the addition of these compounds to produce any recovery once the action potential had been abolished by arsenite.

With regard to the more specific question of hepatitis, Messinger and Hawkins (1940) have recently shown that a high-protein diet can prevent bilirubinaemia and liver damage in dogs after weekly intravenous injection of Mapharsen (3-amino-4-hydroxyphenylarsenoxide hydrochloride); a high fat diet, on the other hand, appears to increase the degree of liver damage. High-protein diets have also been shown to be effective in protection against other types of chemical hepatitis. As early as 1919 Davis and Whipple showed that skimmed milk or commercial casein was of value in protecting against liver injury by chloroform. More recently, Miller, Ross, and Whipple (1940) and Miller and Whipple (1942) have demonstrated that methionine, and to a lesser extent, cysteine and cystine, also protect; the non-sulphur-containing amino-acids confer no protection, and large doses of choline given before the period of chloroform anaesthesia also fail to prevent liver damage. They suggested that methionine, cysteine, and cystine act by supplying SH radicles for the formation with chloroform of non-toxic mercapturic acids.

In view of the work discussed above, relating the detoxication of arsenical compounds to SH groups, it is possible that the protective action of protein noted by Messinger and Hawkins (1940) is also in reality due to the content of sulphur-containing amino-acids. In this connexion it is of interest to recall that as early as 1916 Westrope had claimed that a milk diet, the casein of which is now known to be rich in methionine, given 24 hours prior to the administration of arsphenamine, reduced the immediate toxic effects of the drug.

It was therefore decided to study the effect of the oral administration of certain sulphur-containing amino-acids on the course of post-arsphenamine jaundice, and both cysteine and methionine have been used for this purpose. Cystine has not been employed owing to its insoluble nature and to the fact that SH groups would have to be formed inside the body from it, a transformation which might not be working optimally in an already damaged liver; the effect of cystine on arsphenamine liver injury in dogs has indeed already been shortly reported on by Craven (1931). In the doses given it was found to be without protective action; it must, however, be pointed out that it was apparently given only to dogs kept previously on a high carbohydrate diet.

Though the administration of cysteine or methionine might theoretically be beneficial by virtue of the SH group of cysteine or that derived from the CH_3S group of methionine combining with and removing arsenic from the liver, it must not be forgotten that an entirely different mode of action may be concerned, inasmuch as these acids may act by providing SH groups, attached to the appropriate amino-acid residue, for re-synthesis of essential SH proteins previously inactivated either by arsenic or by some non-arsenical infective agent.

Inter-relationship of methionine, cysteine, and choline. The interpretation of any effect observed with methionine is of course complicated by the other role exerted by this amino-acid in the prevention of certain fatty livers of dietary origin. From a therapeutic point of view there is a theoretical advantage in using methionine, because it serves at least three purposes in the body. It is itself a constituent of proteins. It is known to be a precursor of cystine in the body, for animals will form sufficient cystine for growth when given methionine as the sole source of sulphur in the diet (Womack, Kemmerer, and Rose, 1937). Finally, methionine has been shown to act as a methylating agent (du Vigneaud, Cohn, Chandler, Schenck, and Simmonds, 1941) in the sense that it can be substituted for choline; in the rat 10 mg. of methionine have been shown to be equivalent to 2 mg. of choline (Channon, Manifold, and Platt, 1940). There is evidence in the literature that giving cystine without extra choline is dangerous both to the liver and the kidney in some animals. The pioneer work of Best and his colleagues (see Best and Lucas, 1943) showed that choline in the diet will control the formation of excessive fat in the livers of rats; it is also known that proteins can exert this action, particularly from the investigations of Channon and his colleagues (see review by McHenry and Patterson, 1944). Proteins vary in their effectiveness in this respect; their action seems to be mainly due to the opposing effects of cystine which increases and of methionine which decreases liver fat (Tucker and Eckstein, 1937). Definition is given to the problem by stating that as little as 4 mg. of cystine added to the daily diet of a rat can profoundly influence fat deposition.

In the case of the kidney there has long been evidence that cystine feeding may be dangerous; Curtis and Newburgh (1927), especially, demonstrated conditions under which additions of 0·5 per cent. of cystine to the diet of the rat were harmful. More recently Griffith and his colleagues (Griffith and Wade, 1939, 1941) found that whereas cystine added to the diet would produce haemorrhagic lesions in rat kidneys, the lesions could be controlled either by addition of choline (2 mg. daily) to the cystine or by substitution of methionine. The lesions occurred even on diets not containing abnormal amounts of fat. It was a curious feature both of the kidney experiments and of those of Channon, Manifold, and Platt (1940) upon the liver that increase of cystine beyond a certain level did not necessarily increase the severity of the lesions. Another aspect of this subject was raised by György and Goldblatt (1939, 1942), who found that a cirrhosis of dietary origin, with

acute diffuse necrosis, was increased by cystine and diminished by choline; quite recently Himsworth and Glynn (1944) have stressed the importance of methionine in the prevention of liver damage.

From this brief account it seems clear that methionine is a sulphur-containing amino-acid likely to be of special value, whereas there may be objections to cystine. If the latter is largely reduced to cysteine in the body, the same theoretical objection would apply to cysteine; against this, however, it must be mentioned that Putnam and Hoefer (1939) gave up to 5 gm. of cysteine daily to men for periods varying from six months to over two years without obvious harmful results.

Experimental Details

The effects of three different dietary supplements have been studied.

1. The oral administration of cysteine ester hydrochloride, prepared from naturally occurring cystine extracted from human hair. This was given for seven days in two daily 1 gm. doses, taken with half a glass of water half an hour before the morning and evening meals. In the first few cases cysteine hydrochloride together with 300 to 400 mg. of sodium bicarbonate was used instead.

2. The daily administration of 60 gm. of casein, made up in biscuits, for seven days. The biscuits were prepared as follows: 566 gm. of casein (Glaxo, alcohol-extracted ashless) and 283 gm. of margarine were rubbed into a fine mixture (as for pastry); 255 gm. of Lyle's Golden Syrup were then added and the whole kneaded until it became a firm dough. The dough was rolled out and small biscuits (diameter $1\frac{3}{4}$ in., thickness about $\frac{1}{8}$ in.) were cut. The biscuits were baked in a moderate oven for about 15 min.; when cooked they varied in colour from pale biscuit to brown. Ten biscuits contained 55 to 60 gm. of casein.

3. The oral administration of dl-methionine.

Preparation of dl-methionine. Methionine has a very low solubility in water and is not conveniently taken in solid form, either as a powder or in capsules. It was accordingly made up with addition of dilute hydrochloric acid in the proportion of 10 gm. of crystalline methionine to 141·5 c.c. of water containing 2·8 c.c. of concentrated hydrochloric acid; the amino-acid was usually dissolved by warming. This solution contained 2 gm. of methionine per fluid oz. For administration an appropriate amount was diluted with about three volumes of water and sufficient sodium bicarbonate (5 gr. to half an ounce of the concentrated solution) added for neutralization. The methionine will remain in solution sufficiently long if the dose is taken without unreasonable delay.

From the start of the experiment it was realized that mild cases of jaundice, with their usually rapid rate of recovery, were unsatisfactory subjects for an adequate trial of the value of treatment. It was decided therefore to treat only the more severe cases with the amino-acids. Throughout the

trial treated patients (that is, those receiving the dietary supplements) alternated with controls, and at no stage in the work has a series of fresh cases been put on treatment without simultaneous observation of new controls. From May to August 1943 cysteine (as the hydrochloride of ester hydrochloride) was given to the treated patients, while from August to October 1943 patients were treated in rotation with either cysteine or casein (in the doses described above), or were used as controls. Methionine, prepared for administration as already described, was given to a first series from November to December 1943 in three doses of 2 fluid drachms and one of 4 fluid drachms daily, that is a total of 2·5 gm. of methionine daily for seven days, and to a second series from January to March 1944 in doses evenly spread throughout the day totalling 5 gm. daily for five days, followed by half that amount for a further five days. The majority of the patients had received neoarsphenamine, but a few, particularly towards the later stages of the investigation, had been treated with Mapharside. In most of the cases the jaundice developed round about the fourteenth week after the first intravenous arsenical. On commencement of hepatic symptoms treatment with arsenic and bismuth was stopped; bismuth was resumed as soon as recovery was manifest. All the patients were kept in bed until the serum-bilirubin level had fallen to below 5 mg. per 100 c.c. and were not allowed up fully until it fell below 2·5 mg. per 100 c.c. The routine 'fat-free' diet, somewhat unimaginative because of the limitations of war-time, and varying slightly from season to season, consisted in the main of lean meat or boiled fish once a day, a little skimmed milk, cheese, bread and jam without butter, vegetables, and tinned fruit. A normal diet was resumed when the icterus had almost disappeared and the patient was clinically well. Apart from the restriction of diet the only treatment given was the cysteine, casein, or methionine in the experimental cases. Usually transfer to a Convalescent Depot for rehabilitation for three to four weeks was then arranged, and at the end of this period the patients were seen by us again before return to duty. If relapses took place during this time the patients were referred back to hospital.

Clinical Details

The clinical picture of jaundice occurring during arsenotherapy is a familiar one. Stokes, Ruedemann, and Lemon (1920) gave a full and admirable description which would apply equally well to our series. The peak of incidence of jaundice was between 90 and 110 days after the first intravenous arsenical; 50 per cent. of the cases had occurred by the 120th day and 80 per cent. by the 180th day; the remaining 20 per cent. were spread over periods up to 14 months.

Vague complaints of feeling unwell or of stiffness in the joints may precede clinical icterus by as long as six weeks; during this time while there is no rise in the serum-bilirubin, excess of urobilinogen may be demonstrated in the urine by a positive Ehrlich's aldehyde test. In most cases the prodromal

period lasts about seven days. There may be any combination of the following symptoms: lassitude, pain in the joints (particularly in the shoulders), nausea, vomiting, anorexia, epigastric pain, flatulence, and coryza. Diarrhoea was unusual. In a few cases transient skin rashes were seen, erythematous, urticarial, or purpuric in nature. It was difficult to decide whether these eruptions resulted from sensitivity to arsenic or were signs of metabolic disturbance, but we formed the opinion that the second possibility was the more likely and that the resumption of arsenic in small increasing doses after an interval of three to four months was justifiable. Unfortunately none of the patients returned to our care at this time to enable this theory to be put into practice. A surprising number of patients were symptomless both before and after the onset of jaundice.

The establishment of clinical jaundice often marked the end of subjective symptoms, even although the colour might continue to deepen for some days. Confinement to bed after the first few days was very reluctantly accepted by many patients. A febrile reaction was not uncommon in the patients who reached us early in the disease. Enlargement of the liver was usual in the moderate or severe cases. The spleen was palpable in 31 of the 150 cases in Group A, but in none of these cases was the enlargement considerable. An initially palpable spleen was invariably associated with some degree of fever. In some cases, even after otherwise apparent clinical cure, some degree of splenic enlargement persisted. There appeared to be no relationship between enlargement of the spleen and enlargement of the liver or severity of the jaundice. Two patients had general enlargement of the lymph nodes with negative Paul-Bunnell tests. Ascites was found in five of our patients. Recovery was prompt in four, but the fifth had progressive liver enlargement over a long period of time and was discharged from the service as a case of cirrhosis. Three patients developed a mild peripheral neuritis (Lescher, 1944). Two patients developed severe zona during the course of the jaundice. The incidence of jaundice has been so high in patients receiving arsenotherapy that it is not possible to discover any relationship between jaundice and the frank arsenical dermatitis which occurred in a few of our patients, usually some weeks before the onset of jaundice. Several cases of jaundice arising in the first three weeks of arsenotherapy were seen; these have not been included in the present assessment. The aetiology in this type of case appears to be different, being associated with the sensitivity phenomena of 'the ninth day' originally described by Milian (1920) and fully discussed by Peters (1941). The pathological findings in this type of jaundice have been described by Gutman and Hanger (1941).

Exacerbation and relapse. The course of recovery was in most cases smooth and uneventful, but was interrupted in 25 of the 150 cases in Group A and in five of Group B by an exacerbation of the disease. This was accompanied by the familiar prodromal symptoms, with one marked difference, namely, that a sharp attack of diarrhoea was a common feature. Naked eye examination of the urine showed the reappearance or increase of bile with a coincident

rise in the serum-bilirubin, followed in 24 hours by deepening jaundice. The time of onset of these exacerbations was variable, occurring from the sixteenth to the fiftieth day after the original attack, and being in half the cases between the twentieth and thirtieth day. Exacerbations occurred at all stages of the disease, early and late, and when recovery was almost complete. It was not possible to predict which patients were likely to suffer from, nor to discover any cause of, the exacerbations. As far as is known, none of these patients relapsed after discharge from hospital. It is difficult to draw a distinguishing line between exacerbation occurring during the course of the disease and relapse after an interval of apparent well-being. We have arbitrarily defined relapse as a recurrence of symptoms and signs after discharge from hospital, and confined the term exacerbation to the cases described above.

The causes of exacerbation and relapse are not understood. Further attacks of jaundice in patients receiving anti-syphilitic treatment are not uncommon, and may occur within a few weeks of apparent recovery or after many months. Where treatment with arsenic is resumed and is promptly followed by jaundice, it is tempting to assume that the liver damage in the original attack was such that no further arsenic could be tolerated. But arsenic cannot be the precipitating factor in those patients in whom relapse occurs at varying intervals without the resumption of arsenotherapy. It may be that the inability of a liver which has been damaged or has not completely recovered from an attack of jaundice to tolerate alcohol or other foods, particularly those of a fatty nature, may, like arsenic, precipitate relapse.

It has been suggested by some workers that super-infection with the virus of infective hepatitis may be the cause of relapse. Marshall (1944) stated at a meeting of the Royal Society of Medicine that in his experience relapses occurred after an interval of about 30 days only when the patients had been treated in wards where cases of infective hepatitis were to be found. This theory has been recently amplified by Beattie and Marshall (1944) whose views may be summarized as follows:

1. An attack of infective hepatitis confers complete immunity. On the other hand, Witts (1944) states that recurrence of jaundice will appear in about two per cent. of the cases. Hartfall (1944) states that the occurrence of relapse of this condition is within his experience.

2. By analogy it might be expected that an attack of post-arsphenamine jaundice would confer similar immunity.

3. Relapses which occurred in their series were explained mostly on the grounds of a subsequent infection with infective hepatitis.

We consider that our evidence does not support these views for the following reasons. It is not uncommon for more than one relapse to occur in the same patient. This was the case in five patients in our series. There was no evidence that any patients who relapsed under our care were contacts of cases of infective hepatitis. It may be added that one of our patients

who suffered from post-arsphenamine jaundice, and subsequently relapsed, gave a history of an attack of 'catarrhal jaundice' 10 years before, at the age of 14 years.

Results

In all, 468 cases of jaundice occurring during arsenotherapy for syphilis have been studied. As already pointed out, it was decided to give amino-acids to the more severe cases only. The series has, therefore, been divided into two groups (Table I):

Group A, comprising all cases having serum-bilirubin values of over 8 mg. per 100 c.c. at any time during the disease.

Group B, the remainder, comprising the less severe cases.

A number of the cases in Group A came under observation late in the course of the disease. It was decided, therefore, to draw an arbitrary line, and to include in the analysis only those cases which had been jaundiced for

TABLE I

Number of Cases studied

	Group A	Group B	Group A rejects
Controls (1st series)	17	23	2
„ (2nd series)	40	225	9
Cysteine (1st series)	15	6	8
„ (2nd series)	26	15	3
Methionine (2·5 gm.)	11	4	7
„ (5 gm.)	22	1	4
Casein	19	7	4

Total	Group A	150
„	Group B	281
„	Group A rejects	37
		468

TABLE II

Summary of Results obtained in all Group A Cases

	Number of cases	Number of days from start of jaundice to time when serum-bilirubin fell to below 4 mg. per 100 c.c. with no subsequent exacerbation
Controls	57	25·7
Cysteine	41	21·3
Methionine	33	19·7
Casein	19	32·9

	Percentage number of cases in which serum-bilirubin fell to below 4 mg. per 100 c.c. with no subsequent exacerbation, in the following number of days, calculated from the onset of jaundice				
	Less than 14 days	14 to 20 days	21 to 27 days	More than 27 days	Percentage down in under three weeks
Controls	10·5	24·5	26·5	38·5	35
Cysteine	12	51	12	24·5	63·5
Methionine	21	45·5	21	12	66·5
Casein	10·5	26	10·5	52	36·5

TABLE III

Analysis of Group A Cases

Mean Values for Group A Cases, that is, all cases having serum-bilirubin values of over 8 mg. per 100 c.c. at any time during the disease

	Number of cases	J_1–SB_1	J_1–T_1	SB_1 to less than 4	J_1 to less than 4
Control (1st series)	17	6·5	—	20·8	27·2
„ (2nd series)	40	4·7	—	20·4	25·2
Cysteine (1st series)	15	5·5	9·3	15·0	20·4
„ (2nd series)	26	4·6	5·9	17·2	21·8
Methionine (2·5 gm.)	11	6·6	9·8	14·0	20·6
„ (5 gm.)	22	4·5	8·6	14·7	19·2
Casein	19	5·6	9·0	27·2	32·9

	Number of cases	Number of cases in which the serum-bilirubin level fell to below 4 mg. per 100 c.c. with no subsequent exacerbation, in the following number of days calculated from the onset of jaundice: Less than 14 days	14 to 20 days	21 to 27 days	More than 27 days	Percentage down in under three weeks
Control (1st series)	17	1	4	4	8	
„ (2nd series)	40	5	10	11	14	
Cysteine (1st series)	15	0	11	2	2	
„ (2nd series)	26	5	10	3	8	
Methionine (2·5 gm.)	11	1	4	6	0	
„ (5 gm.)	22	6	11	1	4	
Casein	19	2	5	2	10	
Expressed as Percentages:						
Control (1st series)		6	23·5	23·5	47	29·5
„ (2nd series)		12·5	25	27·5	35	37
Cysteine (1st series)		0	73·5	13	13	73·5
„ (2nd series)		19	38	11·5	30·5	57
Methionine (2·5 gm.)		9	36	54	0	45
„ (5 gm.)		27	50	5	18	77
Casein		10·5	26	10·5	52	26·5

less than 14 days before coming under our care. By this means those cases arriving late in the disease and already nearing recovery were excluded. Obviously it was not possible to obtain an accurate date for the onset of jaundice in all cases, but the date when evidence of jaundice was first noticed by the patient or his medical officer was accepted as the date of onset. These dates were elicited by careful questioning, and it is thought that most of them were accurate within two days. Cases that were treated in the course of a relapse or were undergoing their second attack of post-arsphenamine jaundice were also rejected. From Table I it is seen that there were in all 37 'Group A rejects'.

Table VI gives the following data for each case:

1. The initial serum-bilirubin level on admission to hospital.

2. The number of days from the onset of jaundice to the first estimation of serum-bilirubin (J_1–SB_1).

3. The number of days from the onset of jaundice to the first day of treatment with amino-acid (J_1–T_1).

4. The number of days from the first estimation of serum-bilirubin to the time when the serum-bilirubin level fell to below 4 mg. per 100 c.c., with no subsequent exacerbation (SB_1 to less than 4).

5. The number of days from the first day of jaundice to the time when the serum-bilirubin level fell to below 4 mg. per 100 c.c., with no subsequent exacerbation (J_1 to less than 4).

The final analysis, given in Table II, is presented in two ways:

1. The mean number of days from the first day of jaundice to the day when the serum-bilirubin level fell to below 4 mg. per 100 c.c., with no subsequent exacerbation.

2. The number of cases in which the serum-bilirubin level fell to below 4 mg. per 100 c.c., with no subsequent exacerbation in (*a*) less than 14 days, (*b*) 14 to 20 days inclusive, (*c*) 21 to 27 days inclusive, and (*d*) more than 27 days.

Table III gives a more detailed analysis of the cases in Group A. As already pointed out, these comprise two series of controls and two series of cases treated with cysteine covering different periods of time, and two series of cases treated with methionine with different levels of dosage.

From Table IV it will be seen that there was considerable variation in the initial serum-bilirubin levels at the time of admission to hospital even among the cases in Group A. A further analysis (Table IV) is therefore given of Group A cases of roughly comparable severity at the time of admission to hospital, that is, all cases having an initial serum-bilirubin value of 7 mg. per 100 c.c. or over, this figure being chosen in order to avoid excluding an excessive number of cases and yet at the same time to include the initially more severe cases.

Finally, Table V shows the number of exacerbations during the course of the disease in hospital and the number of relapses occurring after discharge to a Convalescent Depot.

Discussion

The very variable course run by post-arsphenamine jaundice renders the interpretation of any new form of therapy difficult, and it soon became clear that the study of a large number of patients was essential. From the clinical standpoint it was felt throughout the work that treatment with either cysteine or methionine was exerting a slight but definite beneficial effect in that a number of the treated patients reported an immediate subjective improvement. The rate of clinical improvement of the patients closely followed the rate of fall of the serum-bilirubin level, and as the investigation proceeded it became clear that these serial blood estimations were providing satisfactory numerical evidence as to the rate of improvement of the patients' condition. A full statistical analysis of the results of the serum-bilirubin estimations given in Table II will be found in Appendix II. It is apparent from an

TABLE IV

Analysis of Group A cases of roughly comparable severity at the time of admission to hospital, that is, all cases having an initial serum-bilirubin value of 7 mg. per 100 c.c. or over

	Number of cases	Mean initial serum-bilirubin %	J_1 to less than 4
		Mean values	
Controls (1st series)	10	9·4	26·2
„ (2nd series)	19	10·5	19·9
Cysteine (1st series)	13	10·7	18·7
„ (2nd series)	21	10·2	20·0
Methionine (2·5 gm.)	10	10·8	20·1
„ (5 gm.)	16	10·7	19·9

	Number of cases in which serum-bilirubin fell to below 4 mg. per 100 c.c. with no subsequent exacerbation, in the following number of days, calculated from the onset of jaundice				
	Less than 14 days	14 to 20 days	21 to 27 days	More than 27 days	
Control (1st series)	1	3	1	5	
„ (2nd series)	4	5	8	2	
Cysteine (1st series)	0	11	1	1	
„ (2nd series)	5	10	1	5	
Methionine (2·5 gm.)	1	4	5	0	
„ (5 gm.)	3	9	1	3	
Expressed as Percentages:					Percentage down in under three weeks
Control (1st series)	10	30	10	50	40
„ (2nd series)	21	26·5	42	10·5	47·5
Cysteine (1st series)	0	85	7·5	7·5	85
„ (2nd series)	24	48	5	24	72
Methionine (2·5 gm.)	10	40	50	0	50
„ (5 gm.)	19	56	6	19	75

TABLE V

Number of Cases showing Exacerbations and Relapses

	Number of cases	Number of cases having exacerbation	Number of cases having relapses	Expressed as percentage of total number of cases	
				Exacerbation	Relapse
Controls (1st series)	17	6	1	23	5
„ (2nd series)	40 (57)	7 (13)	2 (3)		
Cysteine (1st series)	15	2	0	7	5
„ (2nd series)	26 (41)	1 (3)	2 (2)		
Methionine (2·5 gm.)	11	0	0	12	3
„ (5 gm.)	22 (33)	4 (4)	1 (1)		
Casein	19	5	1	26	5

examination of the figures in Table II that the administration of either cysteine or methionine resulted in a more rapid fall in the serum-bilirubin level, a conclusion that is confirmed statistically. But it will also be seen that the effect is not dramatic; thus, in the control cases, the mean time taken for the serum-bilirubin level to fall finally below 4 mg. per 100 c.c. was 25·7 days; treatment with methionine reduced this by 6·0 days, and cysteine by 4·4 days. In the small number of cases (19) treated with casein the mean duration was as high as 32·9 days.

On account of the wide variations in the duration of individual cases (see Table VI, Col. 'J_1 to less than 4') it was decided to express the results in an alternative form, by calculating the percentage number of cases in which the serum-bilirubin level fell finally to below 4 mg. per 100 c.c. in arbitrary periods of time—less than 14 days, 14 to 20 days, 21 to 27 days, and more than 27 days. When expressed in this form it will be seen that the casein-treated cases approximate very closely to the controls, whereas again the cysteine and methionine groups fared better, the serum-bilirubin levels falling to below 4 mg. per 100 c.c. in under three weeks in almost twice as many of the patients treated with cysteine or methionine—35 per cent. of controls and 36·5 per cent. of casein-treated, as against 63 per cent. of cysteine and 66·5 per cent. of methionine-treated. The same effect with cysteine or methionine is observed if only those cases of roughly comparable severity at the time of admission to hospital are considered (Table IV).

The number of exacerbations and relapses in the casein-treated group agree very closely with those occurring in the control series (Table V); in the cysteine group, on the other hand, only one-third as many exacerbations occurred as in the control group, and in the methionine series about half as many; the incidence of late relapses was approximately the same in all groups.

The failure of the casein to exert any beneficial effect could theoretically be due either to absence of sufficient methionine or to the overloading of the deaminative mechanisms of the damaged liver cells resulting from the absorption of the other amino-acids present in the casein. Though casein is stated to contain from 2·9 to 3·5 per cent. of methionine, it was possible that the special casein used in this work might have been subject to some process damaging to the methionine, or that this might not have survived the baking of the biscuits. The special casein was used because it is generally employed for nutritional experiments where higher purity and freedom from vitamins are required.

Estimation of the methionine present, by the Baernstein method (1936) on casein hydrolysed according to Bailey (1937), gave values of 2·8 per cent. (see Appendix I). Patients receiving the casein biscuits did not therefore get much more than 1·7 gm. of methionine daily, an amount which may not be adequate, and may explain the lack of any noticeable effect. However, more of the biscuits could not easily have been eaten in addition to the normal diet, so that from the practical standpoint the administration of casein in biscuits is not a satisfactory therapeutic measure.

TABLE VI

CONTROLS (1st series, 17 patients). Group A

Initial serum-bilirubin %	J_1–SB_1	SB_1 to less than 4	J_1 to less than 4
10	8	22	30
8	2	30	32
7	9	18	27
4	8	27	35
6	2	25	27
6·8	5	22	27
5	12	17	29
8	5	23	28
6	7	15	22
12	6	43	49
5·6	7	13	20
12	12	23	35
7	0	16	16
12	4	14	18
6	11	31	42
8	5	10	15
10	7	5	12
Mean = 7·9	6·5	20·8	27·2

CONTROLS (2nd series, 40 patients). Group A

7	11	14	25
15	2	20	22
5	8	30	38
6	3	64	67
3	2	20	22
1·5	8	20	28
0·3	0	33	33
13	4	18	22
11	4	12	16
5	2	15	17
8	5	25	30
13	9	13	22
12	5	8	13
11	5	18	23
10	5	6	11
6	6	12	18
5	2	31	33
7	5	10	15
16	8	19	27
1·7	9	20	29
3	0	19	19
3	2	43	45
0·5	0	24	24
6	4	16	20
9	3	9	12
10	3	7	10
6	7	21	28
12	8	18	26
5	2	30	32
11	5	16	21
6	7	39	46
1	8	16	24
9	6	10	16
9	11	7	18
3	0	12	12
5	5	37	41
5·5	0	17	17
9	9	7	15
6	3	30	33
8	4	31	35
Mean = 7·1	4·7	20·4	25·2

TABLE VI (*continued*)

CYSTEINE (1st series, 15 patients). Group A

Initial serum-bilirubin %	J_1–SB_1	J_1–T_1	SB_1 to less than 4	J_1 to less than 4
12	6	13	21	27
5·2	4	10	38	42
16	8	11	9	17
4	7	13	15	22
9	4	7	13	17
10	9	12	10	19
10	2	5	13	15
12	6	9	14	20
8	4	7	11	15
8	5	8	12	17
9	4	7	11	15
10	3	7	15	18
11	6	10	24	30
12	7	10	9	16
12	7	10	10	17
Mean = 9·9	5·5	9·3	15·0	20·4

CYSTEINE (2nd series, 26 patients). Group A

12	4	5	11	15
6	10	11	16	26
9	6	7	13	19
6	4	5	17	21
9	6	7	39	45
6	7	8	21	28
8	5	6	10	15
11	2	3	20	22
3·5	4	5	33	37
9	11	14	9	20
12	5	6	6	11
12	2	3	13	15
7	2	3	15	17
2·5	1	2	33	34
7	1	7	7	8
8	2	3	28	30
8	4	5	8	12
11	6	7	25	31
9	3	4	13	16
11	9	10	31	40
10	1	2	12	13
13	2	3	12	14
9	6	7	26	32
14	6	8	10	16
16	4	5	13	17
9	6	7	6	12
Mean = 9·2	4·6	5·9	17·2	21·8

METHIONINE (2·5 gm., 11 patients). Group A

10	7	9	15	22
9	9	12	9	18
14	7	10	10	17
7	8	15	13	21
10	9	12	17	26
11	8	10	17	25
10	2	5	14	16
6	5	8	21	26
10	10	13	10	20
15	5	8	20	25
12	3	6	8	11
Mean = 10·4	6·6	9·8	14·0	20·6

TABLE VI (*continued*)

METHIONINE (5 gm., 22 patients). Group A

Initial serum-bilirubin %	J_1–SB_1	J_1–T_1	SB_1 to less than 4	J_1 to less than 4
14	5	8	17	22
11·5	4	7	9	13
5·5	2	9	11	13
10	1	4	17	18
16	4	7	30	34
8	5	8	11	16
6	7	11	13	20
8	5	8	9	14
6	1	10	14	15
9	10	13	6	16
7	4	7	14	18
4	4	7	9	13
8	2	5	11	13
11	4	7	9	13
8	5	8	9	14
10	6	11	10	16
6	3	11	28	31
13	7	10	10	17
16	5	8	28	33
3	3	8	10	13
12	10	13	33	43
9	3	9	15	18
Mean = 9·1	4·5	8·6	14·7	19·2

CASEIN (19 patients). Group A

11	4	7	14	18
10	4	7	52	56
6	5	14	46	51
8	3	9	16	19
3	1	5	13	14
12	9	10	15	24
12	4	7	44	48
15	5	8	18	23
14	9	12	11	20
10	12	15	7	19
9	8	11	32	40
8	5	8	39	44
8	10	13	32	42
7	6	9	25	31
8	4	7	37	41
10	4	7	44	48
10	6	9	7	13
9	4	7	61	65
9	3	6	6	9
Mean = 9·4	5·6	9·0	27·2	32·9

Ideally, in a test of this kind it would be desirable to have accurate information regarding the nitrogen balance of the patients, and the methionine and cysteine content of the diet, but owing to the circumstances and the scale on which this trial was carried out such information was of necessity not available.

At the outset of the investigation it was assumed as a working hypothesis that the liver damage in the patients might have been a direct result of the arsenic, and that, in view of the marked ability of the liver to regenerate,

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it should be possible to alleviate the condition if treatment could be applied to remove the arsenic causing the cellular damage. The work which has been briefly reviewed above suggested that simple SH compounds (or compounds from which SH groups could be derived inside the body) might effect such removal if present in sufficient excess. It cannot of course be concluded from our results that our original assumption regarding the direct role of arsenic in the aetiology of these cases is correct, since it is also possible that the beneficial effect observed was due, as was pointed out earlier, to the provision of SH groups, attached to the appropriate amino-acid residues, for resynthesis of essential SH-proteins, previously inactivated either by arsenic or by some non-arsenical cause. Indeed, the work of Salaman, King, Williams, and Nicol (1944) which was carried out concurrently with the present investigation, suggests strongly that the immediate cause was infective in nature, so that the slight effect of the sulphur-containing amino-acids may well have been through a facilitation of cell regeneration, rather than through a direct detoxication and removal of bound arsenic.

Analyses of arsenic in specimens of liver from two patients who had died of post-arsphenamine jaundice gave contents of 0·4 and 2 μg. per. gm. respectively; such amounts are low and in agreement with the idea that the damage is not due to the continued presence of arsenic.

A preliminary report of the present work has already appeared (Peters, Thompson, King, Williams, and Nicol, 1944).

Summary

1. A study has been made of the treatment of patients with post-arsphenamine jaundice by the administration of sulphur-containing amino-acids. The conclusions are based on the treatment of 150 patients selected, for reasons given in the text of the report, out of a total of 468.

2. Three groups of patients were treated respectively with cysteine, methionine, and casein (made up in the form of biscuits), control patients being observed simultaneously throughout. The rate of recovery of the patients was observed clinically and by serial estimation of the serum-bilirubin levels.

3. A slight but statistically significant increase in the rate of return to normal was noted in the patients receiving cysteine or methionine. Casein, in the form and dosage used, brought about no beneficial effect.

4. The interpretation of the results and their possible bearing upon the aetiology of post-arsphenamine jaundice is discussed.

We wish to thank Major-General L. T. Poole, Brigadier T. E. Osmond, and the Officers Commanding the Royal Victoria Hospital, Netley, for having made this work possible. We are indebted to Major C. R. Lane, R.A.M.C., and his technical staff for estimations of serum-bilirubin, to Dr. L. A. Stocken, Messrs. V. P. Whittaker, and G. H. Spray, and the technical staff of the Department of Biochemistry, Oxford, for preparation of cysteine (from hair),

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APPENDIX I

ESTIMATION OF METHIONINE IN CASEIN BISCUITS

(with technical assistance of R. W. WAKELIN)

Methionine was estimated by Baernstein's (1936) later method in which methyl iodide, arising by heating the methionine with hydriodic acid, is washed with barium and cadmium chlorides and then mercuric chloride, and collected in glacial acetic acid-sodium acetate solution containing bromine. The latter oxidizes the methyl iodide to iodate which is titrated in the usual manner. In our hands, the apparatus, exactly copied from Baernstein, gave a recovery of methyl iodide for synthetic dl-methionine of 90·6 per cent., 92·3 per cent. for a Ministry of Supply specimen, and 90·6 per cent. for one of Hoffman la Roche, average recovery 91·2 per cent. Kassell and Brand (1938) found an average recovery of 93·7 per cent. or 2·5 per cent. higher; they stated that some loss occurs through conversion to methyl mercaptan. We have employed a correction factor of 9 per cent. for our estimation of methionine in casein, calculated from our average recovery from pure methionine.

Estimations of volatile methyl iodide upon the A/E casein even after thorough extraction (using as a final step warm benzene), were much too high and showed that the last traces of alcohol or some similar substance had not been removed. After thorough extraction we resorted therefore to

Bailey's (1937) procedure in which last traces of such impurities are removed by appropriate hydrolysis and by evaporating the residue twice to dryness *in vacuo* before using for the estimation. Our values were as follows:

A/E Casein (as supplied) after hydrolysis	2·90%
A/E Casein (as made up in biscuits) after hydrolysis, 2·78, 2·80. Average	2·79%

Percentage values of methionine given in the literature are as high as 3·5. Baernstein gives 3·3 per cent., but Kassell and Brand (1938) quote a value of 2·95 per cent. Slightly lower values were obtained by Lavine (1943), using a periodide method. Our results for the biscuit are slightly low, but not sufficiently so to indicate any substantial loss due to the extraction or the baking. Hence the failure of the casein to function as methionine cannot be explained by destruction of the methionine present by the alcohol extraction or the baking.

APPENDIX II

STATISTICAL NOTE

By M. Greenwood and W. J. Martin

When the *prima facie* inference from a statistical table is not made suspect by the small number of observations or some other weakness, for instance bias in selection, the diagnosis of which is within the province of a statistician, it is mere pedantry to interrupt the reader of a clinical paper by interjections to the effect that certain differences are, or are not, significant. As, however, there must always be limiting cases where it is helpful to have some arithmetical criterion, we give the results of an analysis of the principal data. The reader should not suppose that either the authors of the paper or we neglected other arithmetical investigations, for instance, of the form of the time-charts in the various groups. These, however, did not lead to any clear-cut conclusions, and we do not think that more can be claimed than stated in the text.

The mean number of days from first serum-bilirubin reading to one of less than 4 mg. per 100 c.c. with no subsequent exacerbation (Table II) shows that the groups receiving cysteine or methionine had an advantage over both the controls and the casein group. The differences which are statistically significant, are:

	Differences: (days)
Controls—Cysteine	$4{\cdot}48 \pm 1{\cdot}93$
Controls—Methionine	$6{\cdot}07 \pm 1{\cdot}90$
Casein—Cysteine	$11{\cdot}60 \pm 3{\cdot}92$
Casein—Methionine	$13{\cdot}19 \pm 3{\cdot}91$

The differences between the cysteine and methionine groups, $1{\cdot}59 \pm 1{\cdot}80$, and between casein and the controls, $7{\cdot}12 \pm 3{\cdot}97$, were insignificant. In the

alternative comparison made in Table II the difference between the percentage of cases in which serum-bilirubin fell to below 4 mg. per 100 c.c. in under three weeks were:

Cysteine—Controls	$28{\cdot}3 \pm 10{\cdot}2$
Methionine—Controls	$31{\cdot}6 \pm 10{\cdot}9$
Cysteine—Casein	$26{\cdot}6 \pm 13{\cdot}6$
Methionine—Casein	$30{\cdot}1 \pm 14{\cdot}3$

Methionine differed significantly from the controls and casein, and cysteine was significantly different from the controls, but the difference between cysteine and casein only approached significance (the difference was 1·95 times the standard error).

Table III shows, if both series are combined, that the groups did not differ in the mean number of days J_1 to SB_1 since none of the differences between the four groups are statistically significant.

Treatment was commenced with cysteine almost two days earlier on the average than in the other two groups; this difference $1{\cdot}9 \pm 0{\cdot}8$ was statistically significant. The subdivision into two series shows that no difference existed between the groups of the same treatment group. The apparently large differences between the two series in the percentage of cases where the serum-bilirubin level fell to 4 mg. per 100 c.c. in less than three weeks of the cysteine and methionine groups are within the range of chance fluctuations.

The cysteine and methionine groups had a smaller percentage of cases having relapses than either the casein or controls (Table V), but the only difference which was statistically significant was that between the controls and cysteine, $16{\cdot}2 \pm 7{\cdot}6$. The percentage of cases relapsing varied from three to five per cent. between the four groups, and no significant differences existed between the groups.

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THE PSYCHOGENIC BASIS OF SOME SO-CALLED RHEUMATIC PAINS[1]

By J. FLIND and H. STUART BARBER

In October 1940 a special Rheumatic Treatment Centre was started for Royal Air Force personnel. Its close proximity to a Royal Air Force hospital for the treatment of neuroses offered an opportunity for the study and observation of rheumatic cases both from the medical and psychiatric aspects. For reasons of service policy the Rheumatic Centre was closed some 12 months after its inception. During the period of its existence 120 patients were admitted, including cases of acute rheumatic fever, rheumatoid arthritis, osteo-arthritis, erythema nodosum, and a group of patients whose chief presenting symptom was one of generalized bodily pain. In this last group it was considered that the condition, at the time of our investigation, was in no way a physical one, but entirely a psychogenic reaction. It is proposed in the present paper to discuss some of the findings which resulted from a study of the cases in this group. The investigations were carried out on 42 patients who were admitted under such varying diagnoses as fibrositis, sub-acute rheumatism, myositis, or multiple joint pains. The hysterical reaction on physical examination of the first of these cases led to his being referred to the neuro-psychiatrist as a matter of interest, but as the frequency of hysterical manifestations in these patients became apparent it was felt that they would repay further study. At the same time a clinical picture became more clearly defined and the history soon enabled us to make a fairly accurate forecast of the physical findings.

Clinical Features

History. The symptoms often dated from childhood, and a history of rheumatic fever was not uncommon. Their duration varied from 1 to 15 years, but one patient stated that he had not been free from pain since birth because his mother suffered from rheumatism at that time. The symptoms may be separated into two groups, those of a specifically rheumatic nature referred to the locomotor system and those predominantly of visceral or vasomotor origin. The 'rheumatism' consisted of indefinite pains rarely limited to the joints or any one region of the body. Thus one man complained of pain 'in every joint of his body', another of 'pains all over the body', and a third of 'continuous pains in the arms, legs, and shoulders'. Articular swelling was seldom described by the patients, although in some cases it was

[1] Received December 4, 1944.

tentatively suggested that there might have been slight enlargement of the joints. The majority could not recollect any joint involvement such as would be manifested by swelling or loss of function. In the histories of these patients certain features recurred so frequently that their significance appears to be beyond doubt. These include symptoms suggestive of neurosis, morbid fears about health, a family history of neurosis, irregular employment, and neurotic traits in early life.

Neurotic symptoms at initial examination. Without direct questioning 29 patients complained of some symptom which was suggestive of a functional condition, and this feature often helped to direct further scrutiny towards the psychological aspects of the case. These complaints included 'nerves' or nervousness, feelings of exhaustion, pains behind the eyes, and such symptoms as tremors, 'blacking out', insomnia, dyspepsia, headaches, and dizziness. In one case the emotional over-activity and self pity at the time of the examination aroused suspicion.

Morbid concern over health. Mallinson (1941) has pointed out that Kretschmer in his study of hysteria based on military psychiatric cases of the last war stressed the importance of estimating in each case the 'will to be well' (*Gesundheitswille*) or attitude of the patient towards illness, his readiness or otherwise to succumb to minor ailments and discomforts. Undue concern about health was present in 26 of our cases. A few examples are given below, and other patients in whom a morbid attitude towards illness had persisted throughout life are described later (Cases 1, 2, 10, and 14).

Case 3. Frail child, no appetite, 'mother spent a fortune on me', never allowed to play games, 'mother took too good care of me'.

Case 5. Rheumatic pains since two years of age, unable to go to school until age of seven years, always away from school, 'didn't complete a term of school the whole time I was there'.

Case 8. Now aged 31 years, weakly as a child, eczema for two years when young, 'lot of illness until age of 12 years when I had my tonsils out', rheumatic pains since age of 15 years, has had to give up in the middle of a game of tennis and come off the dance floor on account of pains, greatest period of relief followed a course of liver injections.

Case 12. Now aged 28 years, measles, mumps, and pneumonia in childhood, bronchitis at nine years and was off school for six months, afterwards wore a jacket of thermal wool until adult life, unable to play games, always afraid of catching cold. Since rheumatism at the age of 23 years (for which he had no medical attention) he has been able to undertake only part-time employment in the family business.

Family history. Morbid concern over health was frequently found to have developed in a family setting of illness, near relatives in such families being affected with various complaints, organic or functional, often of long standing. In 20 cases there were instances of this, and the following will serve as illustrations.

Case 7. Father suffers from rheumatism and lumbago, doubled up, has had to use a stick for years, three brothers have all had stomach trouble for years and regularly take McLean's powder, two sisters unduly nervous.

Case 4. Father ill with rheumatism since last war, father's mother suffered from rheumatism and sister from rheumatoid arthritis.

Case 5. Father ill for years with rheumatism and had two operations for gastric ulcer, patient's brother has been confined to bed with empyema.

Another aspect of the family history is the incidence of psychogenic reactions. In those cases in which a reasonably adequate account of the near relatives was forthcoming it was found in 23 that one or other parent was of an excessively worrying over-anxious type to a degree which may be assessed as extreme. In some cases there was evidence of a 'nervous breakdown' in first degree relatives, and in addition other near relatives were undoubtedly neurotic personalities. In one instance a parent had been the subject of a psychosis.

Employment. The lifelong morbid interest of these patients for their health had had a considerable influence on their employment. In eight cases there had been frequent changes of occupation generally with some intervening unemployment, in a never-ending search for the right type of job which would allow adequate regard to the question of 'ill health'. In another eight cases the patients had attained the desired end, and before entering the service were engaged in jobs which carried privileges in the way of extra time off or a specially arranged occupation. The ability of these patients to find an easy, well-paid job with a kind employer was striking. In some instances the family had acquired a business in which several members were able to lead a privileged working life. Where different members of the family shared in the general morbid concern over ill health and ran their own business it was sometimes found that the family might come to lead an extraordinarily restricted existence, as is shown by the following case record.

Case 9, aged 23 years, was admitted to the Rheumatic Centre from a general hospital in March 1941. He had been called up for service during the previous month and his total service amounted to a few days. He gave a history of rheumatism at the age of 16 years the details of which were exceedingly vague. He described his ankles as being painful and swollen. He was working at the time in a sheltered job in a hotel owned by his aunt and was away from work for about a year. He stated that since that time he had never been free from pain for long, and that his feet, legs, hips, and back were particularly affected. About the age of 19 years he attended hospital regularly for 10 months and one leg was encased in plaster for two months. Soon afterwards he developed an eye condition which he stated was diagnosed as iritis, and a doctor told him that it was connected with his rheumatism which he (the doctor) considered must have been particularly severe. Two years later he acquired a small neighbouring hotel which he ran in conjunction with the larger hotel owned by his aunt, and his 'rheumatism' seemed to vary according to how busy and worried he was. Occasionally during the previous year he had been compelled to use two sticks to help him to get

around. Physical examination revealed nothing abnormal and various laboratory tests were negative. In childhood he had been the subject of more than the average amount of minor illness, had lived in a family atmosphere of illness, and had been over-protected. When he was five years old his father had been involved in an accident in the course of which he had been burned. Thereafter the father felt unable to return to his former occupation and after a period of unemployment followed by an unsuccessful attempt to start his own small business he was taken over by the aunt who owned the hotel, who employed him and eventually all the rest of the family. The patient during his school days was a timid, nervous boy who avoided all games. On only one occasion at school had he been nearly involved in a fight, but he had forgotten to turn up for the appointment with the other boy. The incident, he stated, was easily recalled because he remembered how few of the other boys seemed inclined to believe him. This timidity and lack of aggression persisted throughout life. He was proud of the fact that he never lost his temper and the most difficult hotel guest had never succeeded in arousing any sign of irritability in him. It was confirmed that he was intelligent and had done well at school where he had remained until the age of 14 years. His aunt's hotel had grounds amounting to 80 acres and during the first three years there, that is from the age of 14 to 17 years, he had never gone outside the grounds. Afterwards he bought a small car and used to drive slowly and cautiously over short distances. He always felt frightened when circumstances forced him to take a passenger. He had no other hobby and as far as could be ascertained showed no other sign of initiative, with the possible exception that he started to develop a friendship with a girl, but the responsibility became too much for him and the affair terminated within three weeks. The patient's duties in the two hotels had mostly been confined to office work. According to his story he had found difficulty in doing any sustained work owing to his disability, but one gained the impression that within the confines of his hotel life and occupation he was probably an able organizer and efficient worker. The family history showed that the father was a semi-invalid as has been described above. The mother had suffered with one complaint or another for years, firstly phlebitis, then 'threatened with dropsy' and now 'some woman's complaint'. The aunt in whose hotel the family had found refuge had suffered severely from rheumatism since the last war, and the aunt's son had had a 'nervous breakdown' some years ago with an exacerbation after the fall of France, after which he had to give up work for some months. Treatment in hospital induced the patient to give up a hysterical gait, and he ceased to complain of pain when he was promised his discharge from the service. His mental attitude while in hospital was strikingly hysterical. He seemed able to shut out from his mind any ideas connected with the distasteful service in which he had found himself. Towards the end of his stay in hospital one of the brief 'rheumatic' relapses occurred, when some special function was taking place in one of his hotels and he became extremely worried as he pictured the possible mistakes being made in his absence.

Neurotic traits. A clinical psychiatric examination in a co-operative patient usually includes an inquiry about any nervous traits which the patient may have exhibited in childhood and whose presence in numbers, intensity, or persistence to a late age suggests a liability to neurotic reaction under stress in adult life. This matter was, at the time of the present investigation, the

subject of inquiry initiated by Air Commodore R. D. Gillespie and was engaging the attention of the psychiatrists at the Neurosis Centre in relation to neuroses in both flying and ground personnel. The investigation included an estimate of morbid fears (such as fears of the dark, of animals, or of illness), physiological instability (as evidenced by faints, sleep-walking, bed-wetting, stammer, etc.), pattern and degree of visceral response before an ordeal (such as an examination, important match, etc.), temperament, personality, habits, and timidity (questions about games, recreations, etc.). It was found that the great majority of neuroses in ground personnel who had broken down without undue stress showed a high incidence of these features. In the present group of 'rheumatic' cases 16 patients showed a similarly high incidence with the same general distribution. Indeed, there was no discernible difference between the more severe cases of the neuroses and the present 'rheumatic' group, except that in the latter the presenting symptom was the complaint of bodily pain. It seems unnecessary to give a detailed analysis of the findings in all the cases. The following instance is a fair example of what was elicited in the way of neurotic traits in the psychiatric examination of this group.

Case 4, aged 27 years, still showed some fear of dark and was terrified at times when doing guard duty. Uneasy at home alone even in recent years and had experienced palpitations when in this situation, feeling compelled to look in cupboards and under beds. Was frightened when he heard of any friend or acquaintance being ill and was sure that he would develop the same complaint. Disturbed sleep at times and has experienced nightmares at intervals throughout his life, worse lately. Still bites his nails, and showed enuresis till age of 12 years. Tended to worry unduly and become easily depressed and irritable. Had never played games; no interest in them; frightened of water and had never learned to swim. Bullied at school and throughout life had never been able to stand up for himself.

It is of interest to note that on inquiry about timidity it was found that only one of 17 patients was able to swim a few yards; most of them admitted to having tried in the past, but had given it up because it was too frightening.

Physical examination. Physical signs of an active rheumatic infection were conspicuous by their absence, and despite multitudinous aches and pains these patients appeared to be in reasonably good health. In those whose complaint was referred to one or more joints, no inflammatory change, swelling, or other objective sign of rheumatism could be demonstrated. Crepitus was sometimes produced as evidence, but in the absence of limitation of movement or other more positive sign it was discounted. Crepitus may be elicited when there are no painful symptoms referable to the joint affected. In one patient whose symptoms were localized to the hands, the normal widening of the interphalangeal joints was adduced as evidence of rheumatism, and had been described by one medical officer as the spindle-shaped swelling of rheumatoid arthritis. Whether the pain was in the joints or confined to the muscles, the full range of movement could always be

obtained. Active muscular resistance to some movements did occur, but with persuasion and exhortation to relax the complete range was invariably possible. Perhaps the most characteristic sign was found when examining the muscles of the back. Palpation of the glutei, paravertebral muscles, or scapular muscles is normally not a pleasant procedure, but is certainly not productive of pain. Among these cases it resulted in a typical hysterical over-reaction. Excessive writhing, grimaces, and groaning could be induced by palpation of widespread areas extending from the buttocks to the shoulders. Had the pains in truth been so extensive the patients would have been bedridden. Suggestibility is another common finding, and areas of hyperaesthesia could easily be produced. In some cases it was possible to make elicitation of the tendon reflexes and even the abdominal reflexes an apparently painful process. The localization of the more circumscribed tender regions varied considerably during the examination. We were not convinced that any fibrositic nodules could be found in these patients. Two patients displayed gaits of the most bizarre and obviously hysterical type which responded well to psychotherapy. No abnormality was found in the respiratory, cardiovascular, or central nervous systems. The digestive and renal tracts were normal. The erythrocyte sedimentation rates and blood counts were within normal limits in all cases. In some patients it was deemed advisable to confirm the clinical impressions by radiological examination of those joints described as painful, and again no abnormality was disclosed.

Psychiatric examination. From the psychiatric aspect it is proposed to follow the classification suggested by previous writers, namely hysterical, anxiety, and depressive states. Many of the cases showed mixed hysterical and anxiety features and it was not always easy to decide which set of features predominated. In many a varying degree of depression was also present.

Hysterical reactions. In this group there were 17 cases all of whom belonged to ground staff. For the sake of descriptive convenience they will be considered in the following three subdivisions each of which gives some indication of the type of reaction present.

(*a*) Reappearance in hysterical form of what may have been a former organic rheumatic condition.

(*b*) Hysterical prolongation of what was possibly a former rheumatic condition.

(*c*) Hysterical complications of an underlying mental disorder.

Reappearance in hysterical form of what may have been a former organic condition. The feature common to all cases in this section is the history of a previous rheumatic illness from which the patient had, according to his statement, made a complete recovery. All had been free from symptoms for some years and had been perfectly well at the time of entry into the service. Five cases, aged 28, 27, 27, 22, and 19 years, may be included in this section. In one of the patients with a previous history of rheumatic fever the description leaves little doubt of its organic nature. In three patients the description

of the rheumatism makes it difficult to form an accurate opinion in retrospect. In three patients symptoms superficially resembling the previous illness had appeared within a month of entry, precipitating factors being the muscle stiffness arising during preliminary training, the malaise after inoculations, and a mild febrile illness. In the fifth patient symptoms arose during the third month of service when he began to work in the hangars in cold weather. All had been carefully investigated and adequately treated for periods varying from 4 to 12 weeks in Royal Air Force hospitals before admission to the Rheumatic Centre. The following clinical descriptions relate to two of the cases in this section.

Case 1, aged 25 years, came into the service in January 1941 and reported sick four days after starting his preliminary training, complaining of stiffness in the legs and swelling of knees and ankle joints. He was convinced that marching had brought on another bout of rheumatic fever. He spent four weeks in the Station Sick Quarters during which time there was no convincing record of abnormal physical signs. He was admitted to the Rheumatic Centre on the recommendation of a medical specialist. On admission he showed no abnormal physical signs. His numerous complaints included an account, in disgruntled fashion, of the inadequacy of the treatment he had received. At the age of 18 years, soon after leaving school where he had passed the matriculation examination, he had been the subject of rheumatic fever and had been confined to bed for several months, his heart being affected. Thereafter he had remained at home and had not been able to take up any employment for about 18 months. Since an attack of pleurisy at the age of 12 years he had tended to be more than normally interested in his health, and he became more than ever concerned about his physical state after the rheumatic fever. Ultimately he had taken up banking, and although he had been moved to different branches, his health had served as a reason for being kept near home. He had not experienced any further symptoms during the previous five years except, when studying for his bank examinations, a tendency to feel exhausted for which he usually stayed in bed for some days. When he felt inclined he played tennis and cricket and had recently taken up skating. Throughout life he had always tended to avoid the more strenuous sports such as football, and he had never learned to swim. Apart from his abnormal preoccupation with his health he had not exhibited any undue preponderance of neurotic traits in childhood or adult life. He had joined the Royal Air Force shortly before he was due to be conscribed, for purely selfish reasons, on the ground that the billeting, feeding, and general conditions were better than in the other services. At one time he had harboured ideas of volunteering for air-crew, but his dominating father had made him give up the project. There was a family history of psychotic break-downs on the mother's side, and the patient's mother was herself without doubt a hysterical psychopath. His father and mother had separated some years before. His only sister had been an invalid for many years and had died during the previous year at the age of 29 years from what was termed septicaemia. One younger brother was alive and well. Although he did not hide the fact that he wanted to leave the service, he made some response to an explanation about the nature of his symptoms and his subsequent activity in hospital confirmed the wholly psychogenic nature of the condition. He was sent back to duty to try again, although the prognosis for useful service was regarded as poor.

Case 2, aged 28 years, joined the service in December 1940. During his preliminary training he had complained of swelling and pain in the knees and ankle joints. After treatment he carried on for some months, always on selected light duties. In March 1941 he was admitted to hospital with a mild febrile illness of indefinite nature, and on recovery complained of pain in various joints. He received intensive treatment for about 12 weeks and appeared to improve satisfactorily. He was given sick leave before returning to duty, but 'collapsed' with a return of symptoms towards the end of the period of sick leave and was subsequently admitted to the Rheumatic Centre. On admission there were no abnormal physical signs and all investigations were negative. His home life had always been characterized by marked emphasis on illness. He stated that his mother had been crippled with rheumatism nearly all her life and his only brother had been the subject of the same complaint. His mother had always been an over-anxious worrier. In the patient's childhood his father had had to undergo an operation for the removal of a renal calculus. Because the patient was like his father in appearance he was made by the mother to consume large quantities of barley water until adult life, and whenever in the mother's opinion he looked tired or ill he was given an extra dose. As a child he was very nervous, being the subject of sleepwalking, bed-wetting, nightmares, and morbid fears until the age of 12 years, and throughout his life had always been considered too delicate to play games. After leaving school at 14 years he worked in a coalmining job for a year and then joined his father who had started a newsagent's and tobacconist's business. Gradually they extended the number of shops until they owned seven and the patient's occupation became mainly supervisory. He drove round in a car and took little or no exercise. Three years ago his father died and the patient had what his doctor described as a nervous break-down, one of the chief features being sleeplessness which had persisted with some intensity for about a month. Shortly before the death of his father he had been ill with rheumatism for some weeks. It was impossible to judge the nature of his illness, but he had been free from symptoms during the previous two years. Since joining the service he had noticed that the pains always became much worse when he was worried. His progress in hospital was uneven, with frequent complaints of pain and a gait which was often bizarre, but was no obstacle when his interest was aroused. His chief worries concerned his business which his wife was failing to manage satisfactorily, and he did not hide the fact that his main urge was to return to civil life. The prognosis for useful service was considered to be so poor that invaliding was recommended.

Hysterical prolongation of what was possibly a former rheumatic condition. The factor common to all patients in this section is a history of rheumatic illness which had occurred before entry into the service and from which the patient, according to his story, had not completely recovered. It was obviously impossible at the time of our investigation to decide whether or not the original illness was organic in nature. In some cases it was probably neurotic and this would make the present condition a perpetuation of a hysterical simulation. We have assumed that there was originally an organic factor present. Seven cases may be included in this section, their ages being 39, 31, 28, 27, 26, 23, and 23 years. The alleged original rheumatic infection had commenced in the past at periods varying from 16 to 2 years. Four of

the patients had been serving in the Royal Air Force for less than six months and the remainder for less than a year, including periods off duty on account of their complaints. In four of the patients longstanding symptoms of neurosis were conspicuous and in the other three the personality was strikingly hysterical. The following is an example of these cases.

Case 10, aged 27 years, came into the service in October 1940. After a few weeks' preliminary training he began a flight mechanic's course, but almost immediately complained of pains in the back, hips, shoulders, and wrists, a condition which he stated had commenced about a year before joining the service. With spells of light duty and treatment he carried on until he was finally admitted to a Royal Air Force hospital, and later transferred to the Rheumatic Centre in September 1941. On admission, in addition to the above complaints, he stated that he was the subject of headaches, palpitations, and a feeling of exhaustion. There were no abnormal physical signs and all investigations were negative. In childhood he had been the subject of the common ailments although he had never been seriously ill. He had been over-protected by an anxious mother who had kept careful watch over his health until he joined the service. She had made him carefully dry his head if it ever became slightly wet. He had complained of rheumatism-like pains during the year prior to his entry into the service and she had regularly rubbed him with ointment and sent him to his panel doctor so often that the latter lost interest, and he had to go to another doctor in a private capacity. He had been the subject of frequent colds and at times had been afraid to get his hair cut. At the age of 13 years he was supposed to have had 'a touch of rheumatic fever'. He lay in bed for three weeks with pains round the heart, took it easy for several months, and gave up games for good. Since leaving school at the age of 14 years he had been employed as a shop assistant in circumstances which allowed him a few days off at frequent intervals. The family atmosphere of illness was striking. In addition to her mental attitude the mother had had a cough for years, winter and summer. The father it was stated had a recurrent gastric ulcer, as had two other members of his (the father's) family. The patient's only sister 'was always at the doctor, no one knows what is wrong with her'. He appeared to make some response to treatment and explanation, and since it seemed desirable to keep him away from his mother's attention he was sent back to duty, although the prognosis was considered poor.

Hysterical complications of an underlying mental disorder. Five cases are considered to come under this heading, and all of them showed a degree of mental backwardness, the rheumatic condition being considered to be in the nature of a hysterical reaction secondary to the stress of service life on a subject of inadequate mental constitution. In none of the cases were the circumstances in service life such as would have merited the term stress, had the individuals in question been of normal robustness. Their ages were 41, 32, 31, 27, and 27 years; their length of service ranged from two years to six months. On testing by the Stanford revision of the Binet Simon tests three of them showed a mental age of 11 years and one the mental age of 12. The remaining one was definitely 'below average' on testing by the progressive matrices. Four had extremely poor work records in civil life and

three showed long-standing neurotic symptoms in addition to their mental backwardness. The following notes refer to one case.

Case 14, aged 31 years, was admitted to the Rheumatic Centre, having come into the service six weeks before. On admission he complained of 'pain in every joint of the body'. He stated that he 'suffered a lot with his head also', by which he meant headaches, dizziness, and a pumping sensation in the head. In addition he had frequency of micturition which necessitated his getting up several times during the night. He gave a history of rheumatic fever at the age of seven years, went on to relate that he had never been free from joint pain since that time, and that he had had a second attack of rheumatic fever at the age of 25 years which had kept him in bed for four or five weeks and away from work for nearly four months. Since leaving school he had been employed as a farm hand and later as a farm labourer. On account of his rheumatic pains he always felt worse in the summer when the pressure of work was heavier, and throughout the years of his employment had continually sought the lightest work on the farm. He stated that on account of his disability he had been compelled to absent himself from work on many occasions, often for two or three days at a time, and that in recent years he had missed about one day's work in every ten. About a year before he joined the service he left the farm for a more lucrative job of groundsman on an aerodrome where he cut and rolled the grass. He joined the Royal Air Force when he was about to be conscribed, in order to avoid the army. At the age of 14 years, when he left school, he had reached standard V (standard VII was possible). He described himself as having suffered from 'nerves' all his life. He showed numerous neurotic traits and morbid fears in childhood, some of which still persisted. His nocturnal frequency of micturition appeared to be in the nature of an extension of former bed-wetting which still occurred at times. On testing with the Stanford version of the Binet Simon tests his mental age was assessed at 11 years. He was excessively timid and whenever the air raid sirens sounded he was conscious of palpitation, and was unable to go to bed although he lived in the depths of the country and a bomb had never fallen near the village. He could not bear company, could not stand noise, and asserted he had become much more nervous during the past three years since his wife had miscarried and he had been unable easily to find a doctor. The family history showed that his mother and younger sister were regarded as excessively nervous. Three of the mother's brothers were unstable alcoholics. His progress under observation in hospital ran a course commonly seen in this type of patient, the chief features being a more or less complete absence of symptoms when happy and given encouragement and attention, and a relapse when an unpleasant prospect threatened. He was regarded as unlikely to become of value to the service and invaliding was recommended.

Anxiety states. The patients in this group number 22, of whom 20 belonged to the ground staff and two to air-crew. The 20 ground staff patients showed many characteristics similar to the hysterical group, the chief psychiatric differences being that they had exhibited anxiety either in its mental manifestations or physiological accompaniments, or both, at intervals often for years before joining the service. Their length of service before coming to the Rheumatic Centre was revealing, specially as most of them had received long periods of treatment. Eight patients had served for less

than six months, a further seven for less than 12 months, and the remaining five for less than two years. Their age tended to be higher than the average age for serving airmen, 13 being more than 27 years of age and seven under that age. Five patients claimed that their symptoms had started for the first time after joining the Royal Air Force, and in the remaining 15 the pains were alleged to have begun at different times from between 20 and three years before recruitment, although seven of these stated that they were free from symptoms on entry. Four patients had probably been the subject of rheumatic fever in the past. On inquiry about the time and occasion of the beginning of the pains interesting information was disclosed, as in the following two cases.

Case 18. 'Rheumatism has been much worse since my cycle accident three years ago. I have been nervous as well since that time, and also impotent.' The accident in question was not one in which he had been injured to any extent, but he had been extremely frightened.

Case 24. 'My rheumatism started a month after I joined the service—I don't understand it because it was glorious weather—and I felt like I did before, three years ago, after an accident I was in.' In this case the accident was one in which the patient had been driving a car and had killed a pedestrian.

In both cases further inquiry showed that well-marked anxiety symptoms had accompanied the original 'rheumatism'. Such cases are reminiscent of those described by Halliday (1941). In a general way it was found that stress other than the effect of service life had operated to a greater extent than in the hysterical group. Seven of the patients had been exposed to enemy bombing, two had lost relatives in bombed areas, and three had private worries of some magnitude. The two members of air-crew in this group differed in no essential way from the ground staff cases. Their good appearance had tended to cover a well-marked neurotic personality, and both had developed 'rheumatism' symptoms at the initial training centre. The following notes refer to one case.

Case 38, aged 20 years, entered the service for training as a pilot in October 1940. During the first month he experienced a recurrence of alleged rheumatic pains, but he carried on with ground duties while awaiting a vacancy at the initial training centre for air-crew. Soon after reaching the training centre he came under medical observation complaining of pains in the back, joints, and chest. It was noted by the medical specialist to whom he was referred that the pains were worse when he was under emotional stress. He was admitted to the Rheumatic Centre in February 1941. Physical examination showed no abnormal signs and laboratory tests were negative. He was an intelligent man of good physique who had some insight into his condition. He thought that the pains did not merit all the notice that had been taken of them and he felt worse on the occasions when he had felt fear. He himself was chiefly worried about the pain which affected his chest. He related how the same condition had affected him two years before at a time when he was having claustrophobia to an extent which compelled him to leave picture houses soon after entering them, and

to make a long journey to and from the city to avoid underground travel. His condition had improved, but the pains in his chest persisted. On one occasion when he had a severe cold he had sought medical advice and been told that he had a mild bronchitis and muscular rheumatism. The chest pains, which were described as a tightness or a dull pressure, had never been completely relieved. Further investigation showed that he had a well marked phobia for pulmonary tuberculosis, a condition upon which his anxiety had been focused about two years before, and was doubtless connected with the fact that both a near relative and his best friend had died of that disease. At the same time a nurse had made what was to him a disturbing remark about his appearance and suggested an X-ray examination of the chest. Anxiety symptoms had been present in his earlier life. At the age of 8 years he used to panic whenever a sweater was pulled over his head, and at the age of 14 years he had had acute claustrophobia in chapel at school. He had fainted on one occasion after a slight cut. On the other hand, he was not unduly timid and had done some useful work during the early bombing attacks on London, showing a good sense of duty. His mother had a chronically over-anxious personality, and several members of the family were regarded as very nervous. His elder brother was considered to be 'highly strung'. The patient responded well to psychotherapy, and his pains disappeared as his anxiety receded into the background. He was taken off flying duties, but retained in the service. He was seen by one of us a year later when the question of his fitness for overseas service came under consideration. His condition had remained satisfactory and only occasionally had he been aware of mild anxiety feelings. He was working efficiently in a responsible ground occupation.

Depressive states. Three patients, aged 46, 43, and 29 years, are included in this group, and in each case the condition was one of mild endogenous depression, a condition which frequently gives rise to difficulty in diagnosis. Such cases are often missed or misjudged and, since the patient feels very different from his usual self and has difficulty in describing the change which has occurred, it is not uncommon to find some somatic symptoms or signs becoming the focus of attention. The following brief description of one of the patients is given:

Case 41, aged 46 years, was admitted to the Rheumatic Centre in March 1941 complaining of pains in his back, shoulders, and chest, of which he had first become aware in November 1940. He had been treated with massage at the Station Sick Quarters without relief. He also complained of sleep disturbances at this time. He carried on until January 1941 when he became worse and developed headaches of such frequency and intensity that he had to give up his duties. He was a well-developed man of pyknic build, an able, energetic, somewhat obsessional personality who had a good last war record, had been an accomplished athlete, and had held some responsible posts in the coal-mining industry in civil life. He had come back into the service from the Reserve as a machine-gun instructor. His previous health had been good with the exception of a period in hospital in 1926 for what might have been a duodenal ulcer. He remembered, however, two occasions in the past when for no very obvious reason he had been low-spirited for a period extending over five or six weeks. On admission physical examination showed no abnormal signs suggestive of any rheumatic condition. An X-ray examination of his teeth showed one with an apical abscess, the removal of which

did not affect his mental state. In the previous November he had noticed that he was low-spirited and not sleeping as well as usual. By January, when he had to stop work he stated that he felt worse and the difficulty in lecturing had finally 'got him down'. Actually the psychomotor retardation which is so often a feature of this condition was rendering him unable to maintain an orderly sequence of explanation and discussion in his lectures, and after admission to hospital he still experienced this difficulty in thinking clearly when he was reading or writing letters. His ideas tended to be self-depreciatory and his sleep disturbance was of the early waking variety. He described the headache of which he complained as 'a tight band round his head'. The family history was not good, but showed no other illness of this kind. He improved considerably with hospital treatment, but had not fully recovered when he was sent home on sick leave. It was arranged that he should be employed on suitable light duties in the expectation that he would make a full recovery in reasonable time.

Diagnosis. The diagnosis in these cases is difficult. The complaint of pain is something which can be neither proved nor disproved, and even when all physical signs are lacking the physician is rightly loath to assume a psychogenic basis for the patient's complaint. When, as in some of our cases, the start of the condition coincided with a nasopharyngitis accompanied by a slight rise of temperature or a raised erythrocyte sedimentation rate, the diagnosis became impossible until further observation and the progress of the case threw more light on the problem. A further difficulty arises when a doubtful physical sign is elicited. Consequently little exception can be taken to the initial diagnosis in many of these cases, but it appeared to us as time went on and response to treatment was disappointing that the possibility of a psychogenic reaction had not been considered sufficiently often. The indications leading up to the diagnosis are the attitude of the patient, the history of vague pains and doubtful joint involvement, long periods of semi-invalidism and absence from work, and similar conditions prevailing among other members of the family. The absence of objective evidence of rheumatism or any other physical disability and the characteristic reaction of the patient help to determine the true condition. In true so-called fibrositis the pain is localized to a single muscle or group of muscles, hysterical features are not present, and the condition is much more amenable to treatment by physical methods. Long periods of invalidism spread over many months or years do not occur. In fibrositis the blood is described as occasionally showing a leucocytosis, but the sedimentation rate is generally normal. In other conditions of the rheumatic group likely to lead to confusion a raised sedimentation rate will indicate an organic lesion.

Treatment. Short psychiatric methods of treatment were used in the majority of patients of this group. The few who required longer observation and treatment were transferred to the psychiatric beds. Otherwise the methods employed were those of explanation, persuasion, and re-education. Overt hysterical manifestations such as bizarre gaits were usually adjusted at the first interview in the way described by Hurst (Gordon, 1919) in his hysterical cases of the last war, and their progress was maintained by

the physical training non-commissioned officer who had an aptitude for this type of rehabilitation. In addition, a decision had to be made on the desirability of retaining the patient in the service. There were patients whom it was possible to help and who returned to duty. Others were constitutionally unfitted for and unable to adapt themselves to a service life. Others again displayed a degree of selfishness which was at least as conspicuous as their neurosis. There is much difference of opinion as to how far this last group can be or should be compelled to remain in the service. At the time of the present investigation the Royal Air Force policy was to invalid neurotic personnel who were unlikely to be an asset, and consequently about 50 per cent. of our patients were invalided.

Discussion

The psychological factors in rheumatic conditions have attracted considerable interest in recent years and inquiry has proceeded in two main but to some extent interrelated directions. Firstly, some groups of undoubted organic disorders such as chronic arthritis have been investigated with a view to determining whether personality anomalies and emotional states have played a significant part in the aetiology. The work of Nissen and Spencer (1936) and Booth (1937) in America are examples of this method of approach, while Ellman and Mitchell (1936) among others in this country have made a contribution to the problem. Swain and Harris (1938) and McGregor (1939) have stressed the part played by emotional reactions in the aetiology of rheumatoid arthritis, and Halliday (1937) has made the observation that of six patients with rheumatoid arthritis seen in one year three had arisen in the course of anxiety psychoneurotic states. We have not had an opportunity to investigate sufficient cases of arthritis from this point of view, and the present work has no direct bearing on the matter. Secondly, a large group of cases, whose precise organic nature is much less clear, has been studied by a number of workers. The tendency to apply the name rheumatism or fibrositis to conditions in which the chief complaint is one of pain referred to muscles, joints, or bones has resulted in the bringing together of many conditions of widely different nature and aetiology, and it is not surprising to find little general agreement about such an ill-defined group, for which Halliday (1941) has used the term 'non-arthritic rheumatism'. Indeed, until recently American physicians have been inclined to doubt the existence of fibrositis, and in the circumstances it is not unexpected that many cases have been found to present psychogenic features on closer examination.

The suggestion that a number of patients in this group show undoubted psychogenic reactions has commanded increasing agreement, specially with regard to those in whom the disability has persisted for several months. In the last war Hurst (Gordon, 1919) commented on the fact that rheumatism in service patients did not respond to spa treatment as well as it did in civilians.

Gordon (1919, 1939), from work amongst service patients, also made contributions on the hysterical complications of 'rheumatism' and reminded us that Sir James Paget in 1867 had written on the same subject. Halliday (1937) in a review of 145 consecutive patients labelled rheumatism (they included cases of fibrositis, lumbago, neuritis, and sciatica) came to the conclusion that 39 per cent. were incapacitated because of psychoneuroses, and in a second inquiry into 62 cases regarded 37 per cent. as disabled because of psychoneurotic disturbances. Furthermore, he considered that the incidence of psychoneurotic 'rheumatism' rises further to between 40 and 60 per cent. if only those patients are considered who have been on the sick list for two months or more. Gordon also agrees that fibrositis-like complaints are found in hysteria, anxiety states, and depressive states. In a recent medical and psychiatric investigation of 50 civilian and service cases labelled fibrositis, all of whom had been ill for more than three months, Ellman, Savage, Wittkower, and Rodger (1942) found that 35 showed significant psychological disorder, 25 showing hysterical features, seven suffering from anxiety states, and three from depressive states. It is useful to follow McGregor's (1939) description and regard the non-arthritic group as falling into two general categories. Firstly, those cases in which there is suggestive evidence of an inflammatory process affecting muscles, nerves, or periarticular tissues and there may be some general disturbance present manifesting itself by pyrexia and definitely painful areas. Many such cases are termed 'true fibrositis' and in some of them psychogenic factors have been thought possibly to have influenced the onset and been related to exacerbations and prolongations of the condition. Secondly, those patients who complain of pain and stiffness and in whom the physical examination is negative. Here there is more general agreement that many are psychogenic in origin, specially when the condition has persisted for many months. Some show localized pain and stiffness, and in many it has been considered that hysterical prolongation of a mild attack of fibrositis or arthritis may be present. Others complain of generalized body pains, and again the physical examination may be negative. In this last group Ellman, Savage, Wittkower, and Rodger (1942) found that the complaints of 'shifting pain' and 'pain all over the body' were confined to those patients with significant psychological disorder.

The contribution which the psychiatric examination can make to the final diagnosis involves a principle which is not always fully appreciated, namely, that failure to make the diagnosis of physical disease after reasonable observation, investigation, and adequate examination does not necessarily prove that the condition is functional. Positive evidence on the psychiatric side should be forthcoming before such a conclusion is reached. The patient should be the kind of person likely to be the subject of a neurotic reaction, and an adequate reason to explain why he has developed the symptoms at the time should be discovered. The individual is constantly reacting to a frequently changing environment and a neurosis is the result of an interplay between the individual and the stresses to which he is exposed. In the present war various

investigators have found that the majority of service men who break down with neurosis are predisposed to neurotic illness, and that there is a relationship between predisposition and stress. In an airman who shows little or no predisposition a considerable amount of operational stress is required before he develops a neurosis, but in a heavily predisposed subject a slight degree of stress may precipitate the illness. In none of our cases was the stress more than that involved in the vicissitudes and ordinary day-to-day difficulties of service life. An estimate of predisposition in the present series shows that 35 of the 42 cases would have been rated as 'severely predisposed'. From the investigation of control groups in the Royal Air Force there is reason to believe that not more than three per cent. of the normal serving airmen are 'severely predisposed'. We have been unable to examine from this point of view more than 20 of our convalescent rheumatic fever group, but our results approximate to the findings of other workers. Two other factors seemed to us strong evidence against an organic complaint. The first may be termed the easy reversibility of the pains and the way in which they appeared and disappeared with the emotional changes in the patient. This fact was striking in the day-to-day observation of patients in this group. The second was the way in which the pains disappeared in response to psychotherapy in those men of reasonably good personality.

There has been much speculation about the nature of the pains complained of by these patients. Halliday (1941) has suggested that they are purely symbolic in nature as expressive of a state of mind and are being consciously or unconsciously used by the patient as a protest against the situation in which he finds himself, or as an escape from the obligations which are imposed upon him by circumstances. Gordon (1940), on the other hand, states that since some degree of fibrositis is nearly always discoverable in the form of nodules which may be 'sub-symptomatic', it is a matter for argument whether the pain is entirely symbolic, that is, originating exclusively in the sensorium, or whether the patient is using a mild degree of discomfort consciously or unconsciously to achieve an object. Ellman, Savage, Wittkower, and Rodger (1942) consider that the inhibition of aggressive elements in the personality of many of these patients may result in muscular tension felt by the individual as pain and limitation of movement and erroneously interpreted by the examining doctor as fibrositis. It is unlikely that any one explanation will fit every case. As Guttmann and Mayer-Gross (1943) have recently pointed out, pain is a psychobiological phenomenon, and, apart from its anatomical and physiological aspects which have received much attention, it also has a psychological side which has been investigated less thoroughly. We can easily recall many different types of disordered mental states in which various sensations, including that of pain, appear to be one of the accompaniments of emotional change. The generalized mild aching after a prolonged period of nervous tension is not unknown to many of us, as are also the feelings of fatigue in a similar situation. When the latter, due possibly to some persistent conflict in a predisposed subject, appear too readily and fre-

quently, we have the chief presenting symptom of a neurasthenic state or fatigue syndrome of psychological origin. In a similar way aching may become readily and frequently induced. On the other hand, another factor, as Gordon (1936) has pointed out, is the possible variation in the individual's threshold for the appreciation of his bodily sensations. That such sensations are constantly present in many parts of the body can be appreciated during a brief period of introspection, although they rarely enter into the consciousness of the ordinary healthy person. It may be that the threshold for the appreciation of such sensations is lowered in some cases of neurosis.

It is likely that other factors operate in fixing the patient's attention on his bodily sensations. A former organic rheumatic condition with, as it were, a past mental impress of pain seems a likely factor. Similarly a high incidence of rheumatic conditions, real or functional, in the family may play a part as well as the total family attitude to illness. An iatrogenic factor has occasionally appeared. At times the choice may be a conscious one, as suggested by the fact that a few of the patients in the present series ceased to complain of pain and adopted the more conventional neurotic complaints based possibly on a belief that the rate of discharge at the Neurosis Centre was higher than at the Rheumatic Centre. Nevertheless, we regarded none of our patients as frank malingerers. Whatever may be the explanation of the complaint of bodily pains, we felt that we were dealing in these cases with what were primarily neurotic reactions, and from the point of view of diagnosis and treatment we considered that the pains merit no more special attention than, for instance, the tachycardia of an anxiety state.

It might be considered that some of the cases, like those mentioned by Beeson and Scott (1942), were examples of personality changes secondary to generalized fibrositis which had persisted for some time in a subacute state. These writers have described some epidemiological studies on acute myalgia. In their description of a case progressing to a generalized fibrositis they note that a striking effect of the illness was a personality change from a natural cheerfulness to spells of depression and discouragement, and add that the behaviour during the acute stage could easily lead to a mistaken diagnosis of psychoneurosis. We were unable to find any examples of this sequence of events. Rather than any change in personality we found a further development of a personality structure which had always been part of the individual's general constitution. This finding is in agreement with Ellman, Savage, Wittkower, and Rodger (1942), who noted in their series that the possibility of secondary psychological changes due to the prolonged nature of the physical disorder can safely be excluded in the majority of cases, since psychological abnormalities were absent even in the cases of very long standing where the complaint was sufficiently explained by the presence of gross structural lesions.

The most suitable diagnostic term to apply to this group is a problem. The chief difficulty centres round the length of time which may elapse before the diagnosis of neurosis is possible or is actually made, specially in those

cases where a physical disability may have been present at the start. Often the diagnosis of rheumatism is firmly implanted in the patient's mind before the psychogenic nature of the condition becomes clear. The term psychogenic rheumatism, although possibly useful in cases where psychogenic and organic factors are both present, does not seem to be suitable. Similarly the term 'fibrositis' is not, for obvious reasons, desirable. We favour the use of the psychiatric term which is applicable to each case.

Summary

1. About 42 per cent. of patients admitted to a Royal Air Force special Rheumatic Centre over a period of 12 months showed significant psychological disorder.

2. This group of 42 patients who complained of a generalized bodily pain is described. It was considered that the disability was essentially psychogenic.

3. The causation, treatment, and disposal of such cases are discussed and case histories are described.

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ANAEMIA ASSOCIATED WITH UNIDENTIFIED ERYTHROCYTIC INCLUSIONS, AFTER SPLENECTOMY[1]

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With Plates 1 to 5

We have recently had occasion to observe three cases of anaemia, two ending fatally, in which the red blood-cells contained iron-reacting intracorpuscular structures the nature of which has not been determined. They appeared only after splenectomy. We wish to present in some detail studies which have been made of these bodies, and to discuss their possible significance in relation to the anaemias.

Case Reports

Case 1. B. K. History: 713686. A 33-year-old white American housewife was admitted to the medical wards of the Presbyterian Hospital on June 18, 1943, with a six to eight weeks history of increasing fatigue, ankle oedema, and dyspnoea. A moderate degree of jaundice had appeared and persisted, and polyuria had been annoying. One week before admission, she became aware of a sense of swelling and tenderness in the epigastrium. There had been no pain and no recognized fever.

She was born in Pennsylvania, but had moved to New York City at an early age, where she had lived ever since. She had never been out of this immediate neighbourhood, had been unusually well and vigorous, and knew of no possible contact with any toxic agents.

Family history. The patient had three sisters, two of whom had irrelevant medical histories. The third sister had at the age of 12 years a traumatic rupture of the spleen, followed by splenectomy. She is now in another hospital for treatment of bleeding oesophageal varices. The patient had been married twice in the previous 15 years. A son, now 12 years old, by her first husband was in excellent health and presented no abnormalities. His peripheral blood count was normal. Another son, by her second husband, was 6½ years of age. This boy when 13 months old was admitted to the Knickerbocker Hospital because of increasing pallor for two months, and a two-weeks febrile respiratory infection. A transcript of the hospital record describes clinical and X-ray evidence of a diffuse bronchopneumonia. In addition, he was found to have a very large spleen and severe anaemia. A tentative diagnosis of chronic myeloid leukaemia was made, three transfusions were given, and he was discharged two months later, having recovered

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from the pneumonia. Through the courtesy of Dr. N. Rosenthal, we have been able to examine Wright stained smears taken at this time, in which, after long search, three cells were found containing structures illustrated in Plate 1, Fig. 3*b*. This boy is still pale with a slight yellowish tint to the sclerae. He has moderate general lymphnode enlargement and an enormous spleen reaching to the iliac crest. A recent search of blood and centrifuged

TABLE I

Case 1. Blood Counts

Date	Red cells (millions per c.mm.)	Haemoglobin (gm. %)	White cells (per c.mm.)	Polymorphonuclears %	Large mononuclears %	Lymphocytes %	Basophils %	Eosinophils %	Myelocytes %	Platelets (per c.mm.).	Reticulocytes %
21.6.43	1·0	2·8	4,400	62	3	34	—	1	—	79,000	
23.6.43											24·2
8.7.43	1·1	3·8	4,500	72	6	18	2	2	—	84,000	26·0
28.7.43	1·3	4·6	5,400	72	6	18	1	—	3	58,000	20·0
30.7.43	Splenectomy										
2.8.43	2·1	6·0	17,400	75	3	21	—	—	1	151,000	15·2
4.8.43	2·0	6·4	12,500	80	11	9	—	—	—	233,000	16·1
6.8.43	2·1	6·4	15,000	82	4	12	—	2	—	304,000	9·0
9.8.43	1·2	3·5	28,400	71	16	9	2	—	2	254,000	20·6
11.8.43	0·96	3·1	29,800	80	5	13	—	—	2	300,000	21·4
13.8.43	0·90	—	28,600	88	4	8	—	—	—	—	22·6

laked sediment for intra-erythrocytic bodies was negative. A blood count taken at the Willard Parker Hospital showed red cells 4,120,000 per c.mm., white cells 12,400 per c.mm., and haemoglobin 60 per cent. The differential count showed few immature cells.

Physical examination. At the time of admission, T = 101° F., P = 112, R = 23, blood-pressure = 130/40. She was a well-developed, slightly icteric woman. Small soft lymphnodes were palpable in both axillae and cervical regions. Heart, left border of dullness and point of maximum impulse 8 cm. from midline; sounds extremely loud and forceful, soft systolic murmur loudest at apex, regular sinus rhythm. The spleen tip was at the level of the umbilicus, and the liver edge could be felt three fingers below the rib margin. Both liver and spleen were tender. Moderate ankle oedema. Physical examination otherwise negative.

The urine was normal; serum-bilirubin 2·5 mg. per 100 c.c.; phosphatase 2 Bodansky units; albumin 3·8 gm. per 100 c.c., globulin 1·5 gm. per 100 c.c. Kline and Wassermann tests ++++. Cephalin flocculation ++++. Fragility of red cells to hypotonic saline, normal. Blood cultures sterile. Gastric analysis, no free hydrochloric acid after histamine. X-ray of chest showed slight cardiac enlargement, pulmonary congestion in both lung fields, and slight amount of fluid at right base.

Course. The patient remained in the hospital until her death, eight weeks after admission. During her stay, the temperature remained irregularly elevated, ranging between 99° and 103° (Fig. 1). The blood counts are shown in Table I. Nucleated red cells were numerous at all times, on one occasion being six times the number of leucocytes. Smears invariably showed anisocytosis, poikilocytosis, polychromatophilia, and basophilic stippling. The

mean corpuscular diameter was 8·9 μ at one determination, 8·7 μ at another. The fragility to hypotonic saline was not significantly altered as compared with normal control. Reticulocytes were always greatly increased. The total leucocyte count, until splenectomy was performed on July 30, 1943, was within the normal range; after operation, there was leucocytosis until her death. The differential count never showed any striking deviation from the

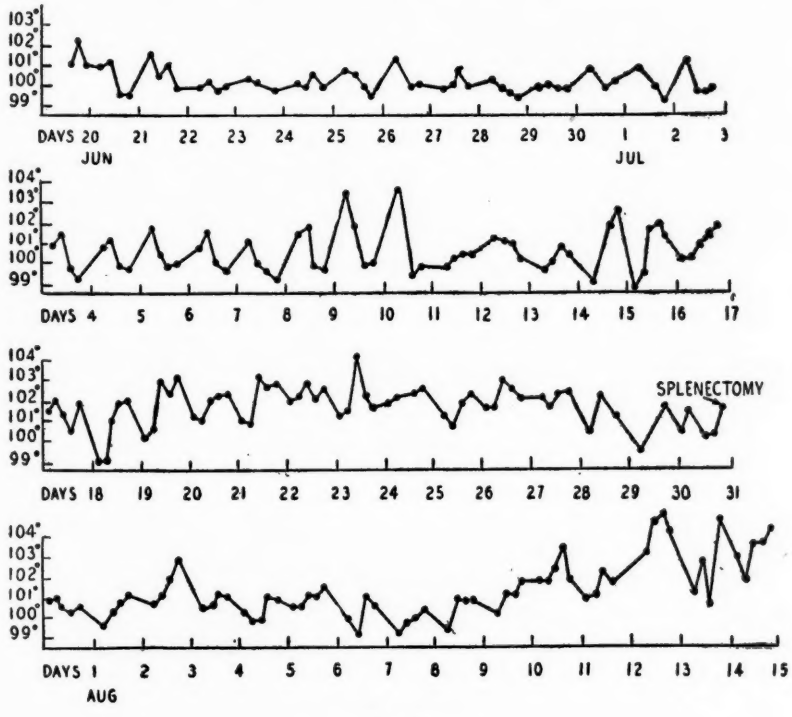

FIG. 1.

normal. There was no eosinophilia. Occasional myelocytes were seen, never exceeding 3 per cent. The platelet counts, before splenectomy, were low. After operation they rose gradually to 283,000 per c.mm. (August 4, 1943). Plasma-proteins were slightly low; there was no alteration in the albumin-globulin ratio. Non-protein nitrogen was not increased, and the urine, save for an occasional trace of albumin, remained normal.

Treatment. The patient, before admission, had received liver extract orally, and beginning on July 6, 1943, was given 1 c.c. of Lilly's crude liver extract and 1 c.c. of Lederle's concentrated extract usually every other day. She received repeated transfusions of whole blood, red cells in saline, and plasma. Because of the repeated positive Wassermann and Kline tests, anti-luetic treatment with bismo-cymol and potassium iodide was briefly tried. All these measures proving without benefit, splenectomy was performed by Dr. Whipple (July 30, 1943). The operation was well tolerated, but had little influence upon the subsequent course. However, examination of Wright stained blood smears after removal of the spleen consistently showed the

presence of many small bodies in the erythrocytes (Plates 1 and 2, Figs. 3 *a* and 4). These will be described in detail below.

Pathology. Sternal marrow biopsy was taken before splenectomy. Smears and sections examined by Dr. Kesten disclosed a predominance of nucleated red cells, especially younger elements. The marrow was very hyperplastic; there were many young blast forms possessing nucleoli and identified as megaloblasts. Mitotic figures were numerous. Megakaryocytes and myelocytes were reduced in number. No haemosiderin was present, and no phagocytosis of red cells by reticulo-endothelial elements. The spleen, removed at operation, weighed 1,100 gm. The cut surface was cherry red, the follicles distinct. There was no evidence of fibrosis. Smears and sections showed splenic elements in normal proportions. The venous sinuses were rather wide, and their endothelial cells conspicuous. No diagnosis was made.

Autopsy report (14203). The examination was performed four hours after death by Dr. Herbert Stoerk. A well-developed, moderately well-nourished woman of asthenic habitus. No cutaneous eruption. Moderately enlarged lymphnodes are palpable in neck, axillae, and inguinal regions.

Peritoneal cavity contains 250 c.c. of clear greenish-yellow fluid. Serosa smooth. No haemorrhage in operative region. Liver extends 14 cm. below xiphoid process, 14 cm. below costal margin in right mid-clavicular line, and 8 cm. in left mid-clavicular line. Right pleural cavity contains 750 c.c. of clear fluid, left contains no fluid. Pericardial sac contains 220 c.c. of clear fluid.

Heart. Moderately enlarged, weighs 420 gm. There are no valvular lesions. There is rather distinct 'tigering' of the trabeculae and papillary muscles of the left ventricle.

Lungs. Right weighs 760 gm., left 680 gm. Right lower lobe almost completely collapsed, dark red, almost non-crepitant on section. Remaining lung parenchyma is pale and moist.

Liver. Greatly enlarged, weighing 3,720 gm., and measuring $32 \times 20 \times 10$ cm. Surface smooth. Organ is firm on section, the lobular structure not distinct. Parenchyma has a distinctly rusty tinge. Bile ducts are patent throughout. Gall bladder contains viscid greenish bile, and appears normal.

Pancreas. Normal.

Adrenals. Cortex contains moderate amount of lipoid.

Kidneys. Normal in size, each weighing 200 gm. They are pale, but not otherwise abnormal.

Pelvic organs. Not remarkable.

Alimentary tract. Normal throughout.

Neck organs. Not remarkable.

Bone marrow of sternum, ribs, vertebrae, and femur is intense deep red.

Lymphnodes. Generalized enlargement, the most conspicuously enlarged being the peripancreatic and aortic nodes. The largest measures 3·5 cm. in length. For the most part, they are of uniform grey colour with a slight brownish tinge, but some present irregular areas of haemorrhage.

Brain and *spinal cord.* Not removed.

Histological examination. The myocardium and lungs show nothing of interest. Liver, architecture well preserved. The liver cells contain abundant haemosiderin, giving a positive iron reaction. There are occasional bile plugs in the canaliculi. The Kupffer cells are large and swollen, often contain phagocytosed erythrocytes, and in Giemsa stained preparation, blue staining bodies to be described below. The portal spaces appear somewhat oedematous, but present no excess of collagen. They contain occasional

eosinophil myelocytes, and rare megakaryocytes. There are a few areas of focal necrosis, the dead liver cells are being invaded by polymorphonuclears. The liver reticulum (Foot-Bielschowsky stain) shows normal arrangement and is not increased.

Bone marrow. Similar to sternal marrow already described, presenting predominantly nucleated red cells, with an abundance of megaloblasts. Eosinophil myelocytes are quite numerous. The endothelial and reticular cells contain bluish staining bodies to be described below.

Lymphnodes. The first examined is moderately enlarged. The cortex consists of normal lymphatic tissue with rather small follicles. Germinal centres are small. The connective tissue of the hilus is oedematous. A few trabeculae show proliferation of the sinus endothelium with formation of minute angioma-like structures. In the second the sinuses are very wide and contain histiocytes, many of which are filled with ingested red corpuscles. There are numerous megakaryocytes, and eosinophil myelocytes are also to be found. The trabeculae appear heavier than normal, and present, in addition to an increase in collagen, a rather marked angioblastic proliferation of the endothelium. In many places the sinuses contain blood.

Blue staining bodies can be demonstrated in Giemsa stained sections, within endothelial cells and histiocytes.

Sections of pancreas, kidney, and uterus show nothing remarkable. The cervix is the seat of mild chronic inflammatory changes. There are minute ulcerations of the vaginal mucosa, with a rather intense chronic inflammatory reaction. There are occasional small papillary formations. Gastric mucosa. One section shows that acidophilic cells are numerous; there is little atrophy. Another section contains no acid cells. Other organs not remarkable.

Anatomical diagnosis. Haemolytic anaemia, cause undetermined; splenomegaly; hyperplasia of bone marrow; focal necrosis and haemosiderosis of liver; icterus; oedema of lungs; ascites; anasarca; granular colpitis.

Case 2. C. R. History: 715843. The patient, a white woman, stenographer, 23 years of age, was admitted to the Presbyterian Hospital on July 19, 1943, and died on September 13, 1943. Her chief complaints were weakness, jaundice, and anaemia for the preceding eight weeks.

Past history. She was born in New Jersey and had always lived there. Family history, irrelevant.

Present illness. Eight months before admission, she had had an attack of vomiting and diarrhoea after eating pork. The symptoms disappeared, but at intervals thereafter there were periods of three or four days when the sclerae were noted to be yellow. The urine was never dark or the stools clay coloured. Eight weeks before admission, fatigue became a prominent symptom. She was given liver, and perhaps iron. Five weeks before admission, she entered St. Peter's Hospital in New Brunswick. The important findings while she was there were—icteric index 75, haemoglobin 12 per cent., red cells 780,000 per c.mm., and white cells 3,600 per c.mm. Transfusions could not be given at first because of agglutination of donor's cells with patient's serum. She was given plasma, glucose, and saline; then nine transfusions, beginning with small amounts to which she reacted with fever and chills. Because of increasing anaemia, she was referred to the spleen clinic and was promptly admitted to the medical wards.

Physical examination: T = 103° F., P = 136, R = 26, blood-pressure = 130/64. Skin of lemon yellow tint. Sclerae jaundiced. No enlargement of lymphnodes. Heart rapid, not enlarged, systolic murmur all over praecordium.

Abdomen soft. Liver felt at costal margin. Spleen two fingers' breadths below costal margin, firm, not tender. Reflexes normal.

Laboratory findings on admission July 19, 1943: Kline test negative, haemoglobin 2·9 gm. per 100 c.c. (20 per cent.), red cells 820,000 per c.mm., white cells 19,600 per c.mm., platelets 171,000 per c.mm., and reticulocytes 19·8 per cent. Differential count: neutrophils 79 per cent., lymphocytes

TABLE II

Case 2. Blood Counts

Date	Red cells (millions per c.mm.)	Haemoglobin (gm. %)	White cells (per c.mm.)	Polymorphonuclears %	Large mononuclears %	Lymphocytes %	Basophils %	Eosinophils %	Myelocytes %	Platelets (per c.mm.)	Reticulocytes %
19.7.43	0·82	2·9	19,600	79	5	12	3	1	—	171,000	19·8
22.7.43	0·74	3·1	9,600	83	2	11	—	1	3	—	39·7
25.7.43	Splenectomy										
28.7.43	1·2	3·8	27,600	88	7	2	—	3	—	242,000	34·0
30.7.43	1·4	4·4	11,800	85	10	4	—	1	—	330,000	32·5
3.8.43	0·74	2·2	31,300	87	3	9	1	—	—	334,000	40·5
4.8.43	1·2	3·6	—	—	—	—	—	—	—	—	—
6.8.43	1·0	3·8	23,500	75	5	14	—	1	5	352,000	55·0
9.8.43	1·6	5·2	28,000	94	—	4	—	2	—	198,000	23·6
11.8.43	2·6	7·8	16,800	93	2	1	1	3	—	—	37·4
13.8.43	1·8	6·5	18,400	81	—	4	2	8	5	265,000	—
16.8.43	0·61	2·5	29,000	80	10	8	2	—	—	—	59·2
18.8.43	1·2	5·2	29,400	78	7	12	1	1	1	276,000	—
19.8.43	1·4	4·9	—	—	—	—	—	—	—	—	—
20.8.43	0·86	2·9	32,400	82	7	8	1	—	2	—	—
23.8.43	1·36	4·8	11,500	73	3	13	1	7	3	—	35·8?
24.8.43	1·96	6·5	10,400	71	3	14	1	9	2	326,000	—
26.8.43	1·3	5·5	10,000	80	8	5	1	5	1	546,000	64·6
30.8.43	1·3	4·8	18,200	60	9	19	4	6	2	—	50·2
1.9.43	1·2	4·5	10,400	85	1	7	4	2	1	629,000	—
3.9.43	1·6	5·5	18,800	83	2	11	—	4	—	—	—
7.9.43	1·4	4·8	—	—	—	—	—	—	—	195,000	—
8.9.43	1·5	5·1	800	—	—	100	—	—	—	—	—
10.9.43	1·4	3·8	200	—	4	94	—	—	2	—	—

12 per cent., mononuclears 5 per cent., basophils 3 per cent., eosinophils 1 per cent. Nucleated reds 72/100 white cells. Patient's blood was found to be Rh positive, in several tests. Sedimentation rate 170 mm. in 20 minutes. Red cells in smears showed marked anisocytosis, poikilocytosis, and polychromatophilia; there were some microcytes, but they did not appear spherical. Serum urea nitrogen 12 mg. per 100 c.c., bilirubin 8 mg. per 100 c.c. Stool dark brown; guaiac test negative; urobilin ++. Urine: albumen + to ++, occasional leucocytes; no red cells or casts; urobilin ++. Variable response of red cells to hypotonic saline.

Course. In the week after admission the patient was given two small transfusions of whole blood, and had chilly sensations with rise of temperature to 105° F. after each. As there was no significant change in her blood counts, which are shown in Table II, she was transferred to the surgical service, and splenectomy performed on July 25 by Dr. Whipple. Report on surgical specimen of spleen (M.P. 4827) by Dr. Homer Kesten was as follows:

'The organ is dark red, moist, weighs 550 gm. The Malpighian bodies vary in size, some being encroached upon by pulp that is rich in blood. About many of them are numerous eosinophils and neutrophils. The pulp cords are wide, packed with red cells, and in many areas they contain numerous mature polymorphonuclears and eosinophils. A little haemosiderin is also present. The outstanding feature in this section is widespread haematopoiesis within

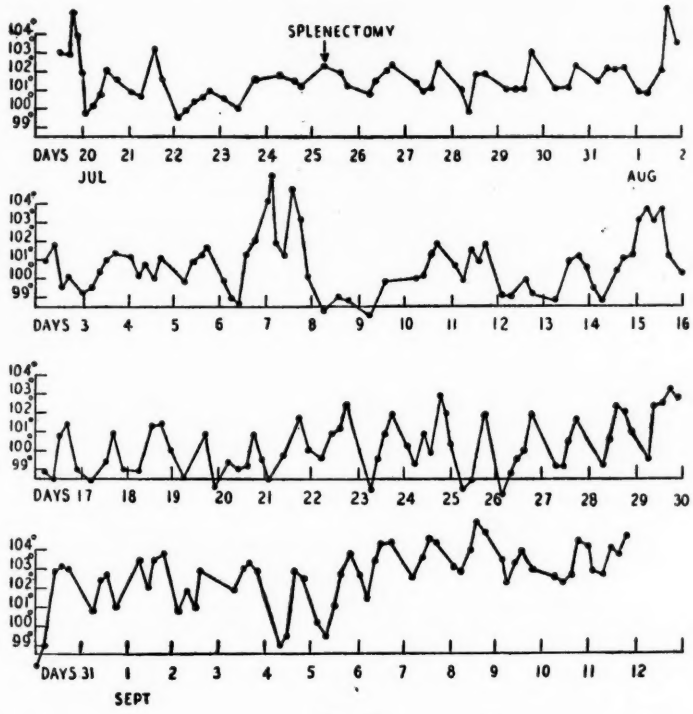

FIG. 2.

most of the venous sinuses. Islands of red-cell formation and of white cells are numerous, the former including erythroblasts and normoblasts, the latter being composed of myelocytes and mature polymorphonuclears. An occasional megakaryocyte is also present. The lining cells of the sinuses are not remarkable. Phagocytosis of red cells by reticulum cells is occasionally seen.'

The patient's condition did not improve after splenectomy. She received many transfusions, usually of 250 c.c., after which the temperature rose immediately to 102° to 105° F. The haemoglobin was as low as 1·5 gm. per 100 c.c. and the red cells on one count as low as 400,000 per c.mm. The leucocytes were usually elevated, at times to 43,000 per c.mm., with 93 per cent. neutrophils. Reticulocytes were high, up to 23·6 per cent. The patient's best response followed administration of red blood-cells suspended in saline. She had no reaction, and subjective improvement was marked but transient. Later, washed cells were injected, and when she was transferred back to the medical service on August 24, her red cells were 1,960,000 per c.mm. In

spite of these episodes of temporary improvement, the haemolytic process continued and the high swinging fever persisted (Fig. 2). On September 8 the white cells were unexpectedly found to be 800 per c.mm.; lymphocytes 100 per cent. The classical features of agranulocytic angina rapidly appeared, the temperature rose to 106° F., the white cells dropped to 100 per c.mm., a gangrenous stomatitis and pharyngitis appeared, and she died on September 13. The bodies, to be described below, appeared in the red blood cells after splenectomy, and were continuously present until death (Plate 1, Fig. 3*c*, Plate 2, Fig. 5).

Autopsy (14222). Performed by Dr. Edith Sproul. *General status.* A very thin, young white female. Irregular areas of ecchymosis over anterior as well as posterior portion of the body. Several small non-indurated crusted lesions 1 to 3 mm. across are scattered over exterior surfaces of arms and legs. The sclera and conjunctiva of the right eye are injected and swollen. No enlargement of superficial lymphnodes. On right aspect of labium majus is a deeply pigmented mole 1 cm. in diameter. No oedema of extremities.

Peritoneal cavity contains 250 c.c. of light-coloured clear fluid. Fibrous adhesions in region of splenectomy.

Thoracic cavity. Small amount of clear fluid in each pleural cavity; 100 c.c. in pericardial sac.

Heart. Weighs 320 gm., no significant lesions.

Lungs. Right weighs 550 gm., left 420 gm. In lateral and posterior portions, parenchyma is boggy, mottled dark purple. Bronchi contain stringy mucoid secretion. The greater part of each lung appears normal in section, but there are partially confluent, bright red areas in posterior halves, sometimes studded with bright yellow dots. No abscess formation or evidence of organization.

Accessory spleen. Near tail of pancreas there is a round encapsulated mass, about 5 cm. in diameter, composed of bright red splenic pulp traversed across the middle by a yellow linear area of necrosis. Extending out from this are fibrous septa which divide the mass imperfectly into several distinct lobules. No follicles are visible, and trabeculae cannot be made out with certainty.

Liver. Weighs 1,960 gm. and is of normal shape. Lobular structure is indistinct. The parenchyma is light orange-yellow in colour, suggesting the presence of abundant haemosiderin.

Gall bladder contains a free pigment stone, 3 cm. in diameter, otherwise normal.

Pancreas, kidneys, and *adrenals.* Not remarkable.

Pelvic organs. Vaginal wall is partly covered with tenacious green, granular, exudate, extending up over vaginal surface of cervix. No other abnormal changes.

Neck organs. Base of tongue, tonsillar region, uvula, and posterior pharyngeal region are covered by thick green exudate, under which mucosa is congested and haemorrhagic. There is marked oedema of aryteno-epiglottic folds and epiglottis. Thyroid and parathyroid not abnormal.

Alimentary tract. Oesophagus shows bile staining and superficial ulceration. Stomach, normal. In second and third portion of duodenum and in scattered areas of jejunum, flecks of adherent, bile-stained exudate are found.

Lymphnodes. Intra-abdominal nodes have distinct rusty colour, suggesting presence of haemosiderin. Elsewhere they are not grossly abnormal.

Bone marrow of sternum, femur, ribs, and vertebrae is moist and bright red.

Brain and *spinal cord.* Not removed.

Histological examination. Heart, one small area of necrosis, involving not more than three fibres, is found; no other significant lesions.

Lung. There is no exudate on pleural surface, but all alveoli contain some inflammatory exudate varying in degree and kind. For the most part it is of delicate fibrin and protein precipitate. In other areas there are masses of bacteria and occasional spore-containing mycelial filaments. There is little polymorphonuclear leucocytic response. Alveolar capillaries are intensely congested, and there are occasional small haemorrhages.

Accessory spleen. Capsule thickened. There is a marked degree of fibrosis through many areas of parenchyma. Sinusoids are small, usually empty of blood, but there is much blood in the pulp cords. The few follicles which can be identified are deficient in lymphocytes. Extending across mid-portion of section is an area of necrosis staining deeply with eosin, and with much nuclear fragmentation. At the periphery of this is well-formed collagenous tissue with haemosiderin and haematoidin in abundance, and occasional iron incrustations of elastic fibres. Haemosiderin is abundant in phagocytic cells within the pulp. There are very few areas of haematopoiesis. Giemsa stain brings out several additional features. 1. Mycelial-like filaments, irregularly distributed through pulp. 2. Minute, deeply blue-stained coccoid and often diploid bodies in the cytoplasm of the endothelial cells lining the sinusoids (Plate 2, Fig. 6). 3. No bodies are recognizable within or upon the red cells, but these are less well preserved than in the operatively removed spleen, where they are readily identified.

Liver. The capsule is normal. There is some variation in the size of the lobules, chiefly due to collapse and fibrosis in scattered zones. Where it is present, an area occupying about one-third of the lobule includes no liver cells, has delicate fibrous tissue with capillaries, and many phagocytic cells containing a brown refractive coarse pigment. There is no active necrosis of liver cells. For the most part these areas are exactly in the centre of the lobules, but occasionally they are present in the mid-portion. Elsewhere liver cells are of average size, but frequently contain small vacuoles. A moderate amount of coarse refractive pigment is present in many of the liver cells as well as in Kupffer cells. There is no enlargement or cellular infiltration of the portal spaces. Giemsa stain: the Kupffer cells contain, in addition to refractive brownish pigment granules of varying size, smaller deeply blue stained bodies, sometimes in diploid or tetrad form. Iron stain: in addition to the ferruginous pigment, there are minute bodies within the Kupffer cells which stain with fuchsin counterstain; there is abundant haemosiderin within the liver cells.

Pancreas. No significant change.

Adrenals. The cortical cells are depleted of lipoids.

Kidneys. Not remarkable.

Vagina. The epithelium is desquamated and the surface covered by thick masses of bacteria, beneath which is a slight mononuclear reaction, accompanied by intense congestion. The vaginal surface of the lesion shows similar changes. Uterus is normal.

Small intestine. The mucosa and submucosa are congested; there are areas of erosion with more or less complete loss of glandular tissue and replacement by bacteria and long, spore-bearing mycelial filaments. There is little cellular response, but a few capillaries in the vicinity are occluded by fibrin. A section of colon shows similar changes.

Abdominal lymphnodes. The entire node is depleted of lymphocytes, and there is a mild diffuse increase in supporting stroma. A few areas of complete

necrosis, with nuclear fragmentation and coagulation, occur beneath the capsule. Many mononuclear cells throughout the node contain refractile yellow pigment. Lymph channels are widely dilated, but they are not lined by especially prominent endothelium and they remain empty except for the protein precipitate. A few plasma cells, some with two nuclei, are present. Giemsa stain: occasional blue-staining coccoid bodies are seen within the sinus endothelial cells or within detached mononuclear cells.

Bone marrow from rib, femur, sternum, and vertebrae is similar. It is greatly depleted of haematopoietic cells, intensely congested, and often haemorrhagic. A few megakaryocytes are present. There are many large mononuclear phagocytic cells, but very few cells of myeloid or erythroid series. Giemsa stain: the large histiocytes are seen to be filled with deeply blue staining granules. These range in size from minute coccoid forms to larger bodies the size of a red blood corpuscle. One has the impression that the larger bodies are formed by the fusion of the smaller ones. The granules are spherical and occur over and over again in diploid, less often in tetrad, form, resembling bacterial diplococci. There are no rods (Plate 2, Fig. 7).

In the red corpuscles, in favourable fields, and especially well seen in smears, one may discern bodies identical with those in the peripheral blood. They take a violaceous or purplish-blue stain in contrast to the intense pure blue of the bodies within the histiocytes. The bodies within the histiocytes are Gram-negative.

The two preceding cases are obviously most unusual. They both presented progressive febrile anaemia, with an undamaged hyperactive marrow unable effectively to arrest the progressive anaemia. Both had splenomegaly and neither benefited by splenectomy. Treatment with liver extract and iron was ineffective, and transfusion reactions were severe both before and after removal of the spleen. In both patients, after operation, peculiar inclusions appeared in the erythrocytes. The third case, although somewhat similar clinically and haematologically, is much less severe and does not seem at present to be rapidly progressing to a fatal termination.

Case 3. C. K. History: 719863. A 20-year-old, single, Irish-Polish boy was admitted to the Presbyterian Hospital on September 7, 1943, for investigation of his anaemia and splenomegaly.

Family history. Irrelevant.

Past history. Born and lived in northern New Jersey. Does not know of any previous illnesses. Occupation, stock-yard worker. No known exposure to toxic substances.

Present illness. At 13 years the school physician said that he had a murmur, and restricted his activities. Two years later he was pronounced well, and has exercised without restriction since. No dyspnoea on exertion. Has been pale for past five or six years. No other symptoms. He was rejected by Navy, Marines, and Army because of poor vision, but passed his physical tests in January, 1943. Because of a cold contracted after exposure, he was admitted to the hospital at Camp Dix, where he was told that he had anaemia and enlarged spleen. While at this hospital he had sternal and lymphnode biopsy and various laboratory tests. The red cell count five months ago was said to be about 2,500,000 per c.mm. He was discharged with a diagnosis of splenic anaemia.

Physical examination. Temperature, pulse, and respiration, normal; blood-

pressure = 125/60. A very well-developed and well-nourished white boy in no distress. Skin is oily and pale, but sun-tanned in exposed areas. Nail beds and mucous membranes very pale. No petechiae or jaundice. Heart, left border 9 cm. to left of mid-sternal line in fifth interspace. The sounds are muscular and strong. Blowing systolic murmur heard all over praecordium, transmitted to neck and axilla. No rub. No diastolic murmur. Pulse full,

TABLE III

Case 3. Blood Counts

Date	Red cells (millions per c.mm.)	Haemoglobin (gm. %)	White cells (per c.mm.)	Polymorphonuclears %	Large mononuclears %	Lymphocytes %	Basophils %	Eosinophils %	Myelocytes %	Platelets (per c.mm.)	Reticulocytes %
15.9.43	3·7	7·6	6,400	55	10	35	—	—	—	248,000	1·5
1.11.43	3·7	6·5	6,500	56	6	35	2	1	—	307,000	1·2
9.11.43	3·6	7·0	5,400	49	6	42	1	2	—	—	—
10.11.43	Splenectomy										
12.11.43	3·9	7·6	20,900	78	8	12	1	1	—	215,000	—
15.11.43	3·4	8·3	9,500	77	11	9	1	2	—	409,000	—
18.11.43	3·4	8·0	8,300	59	8	24	3	6	—	606,000	—
22.11.43	3·7	7·7	7,000	34	9	44	4	9	—	966,000	—
27.11.43	3·25	6·8	10,000	38	5	47	4	6	—	—	—
29.11.43	3·7	7·1	8,400	28	20	46	3	3	—	352,000	—
2.12.43	3·7	8·0	7,300	36	14	45	3	2	—	814,000	1·9
6.12.43	3·6	8·0	10,500	43	15	34	5	3	—	764,000	—
21.12.43	2·8	6·8	10,400	38	12	38	5	7	—	—	—
11.1.44	3·6	9·0	9,800	43	12	38	3	4	—	784,000	0·7
5.4.44	3·3	6·5	20,500	59	7	29	3	2	—	802,000	1·9
2.5.44	2·95	7·0	11,600	23	11	60	4	2	—	553,000	2·1
13.6.44	4·3	8·0	11,500	31	19	47	1	2	—	—	1·2
10.10.44	3·6	7·2	13,500	47	13	37	—	3	—	745,000	—

88 per minute. The spleen was firm, and palpable three finger breadths below costal margin. Liver palpable, two to three finger breadths down; not tender. No masses. No visible veins. Lymphnodes not enlarged. Reflexes normal. The red cells at all times showed marked anisocytosis, poikilocytosis, and hypochromia. Nucleated red cells, 1 to 6 per 100 white cells. Mean corpuscular diameter, 8·0 μ, mean corpuscular haemoglobin, 17·6 per cent. (normal 27 to 32), mean cell volume, 70·5 c. μ (normal 80 to 95), mean cell haemoglobin concentration, 24·9 per cent. (normal 33 to 38). Haematocrit, 26·1 to 28·0 per cent. Plasma specific gravity, 1·0245. Plasma proteins, 5·97 gm. per 100 c.c. Blood group 0. Mother Rh positive. Blood fragility, Sept. 16, 1943, haemolysis begins at 0·45, not complete at 0·30; Jan. 12, 1944, haemolysis begins at 0·425, control 0·450; not complete at 0·325, control 0·325. Prothrombin time, normal. Kline test negative. Urine, specific gravity 1,010 to 1,020, trace of albumin, no casts or red cells. Serum proteins (Sept. 16, 1943), 6·6 gm. per 100 c.c., albumin 5·1, globulin 1·6. Urea nitrogen 11 mg. per 100 c.c. Basal metabolic rate +35 per cent. Before operation the temperature several times reached 100° F.

Course. A positive diagnosis, other than anaemia with splenomegaly, could not be made, and since the patient had failed to respond to the usual anti-anaemic measures, splenectomy was performed on November 10, 1943, by

Dr. Elliott. The pathological report (Dr. Homer Kesten) was as follows. The spleen weighs 420 gm. and measures 17 × 9·5 cm. It is rather firm, rubbery, and has a smooth translucent capsule. The parenchyma is dark red, firm, and only moderately moist. Some of the follicles are rather large, with a diameter up to 1 mm. Two spherical accessory spleens, each having a diameter of about 1·7 cm., resemble the main organ.

Microscopy. Malpighian bodies are small, germinal centres ill defined. The parenchyma contains great numbers of erythrocytes, but only a moderate number of nucleated forms. The erythrocytes are undergoing fragmentation, and some of the fragments have been ingested by phagocytic cells. Nucleated cells are of usual type and present in normal proportions. Sinuses, most of them containing blood, are lined by somewhat conspicuous cuboidal cells. There is no significant increase in connective tissue. A few haemosiderin granules are seen in haematoxylin-eosin preparations. With the iron stain, iron-reacting pigment is fairly abundant in the form of fine granules as well as larger masses; connective tissue fibres just outside the endothelial cells lining the sinuses are also impregnated. Giemsa stain: a rare, tiny purplish granule is found within cytoplasm of sinus endothelium.

Cultures. The micro-organisms obtained will be described below.

The patient recovered from the operation without complications, and remained practically afebrile. He has returned to the out-patient clinic several times since his discharge on December 8, 1943. He received three injections of neo-arsphenamine intravenously over a period of six days (0·1, 0·15, 0·2 gm.) without appreciable effect. As appears from Table III, his haematological findings have not materially changed, nor has there been any obvious change for better or worse in his clinical state.[2]

The intra-erythrocytic bodies, to be described in detail later, were first seen on November 12, 1943, two days after operation, and have been present in increasing numbers since. At the last examination, 55 per cent. of the erythrocytes were affected (Plate 1, Fig. 3 *d*, Plate 3, Fig. 8).

Study of the Inclusion Bodies

Bodies in erythrocytes. Since autopsy afforded no satisfactory explanation of the nature of the illness of the first two cases, the blood films made during life were reviewed. In all smears, obtained after splenectomy, bodies such as shown in the accompanying figures (Plates 1 to 3, Figs. 3 to 8) were present in a fairly large proportion of the erythrocytes. With the Wright stain used, they appeared as minute coccoid or slightly elongated structures, taking for the most part a dark reddish-purple or purplish-blue colour, although one could sometimes distinguish a bluish component. The staining in Giemsa solution was identical. Rod forms were occasionally found, but were far less numerous than the coccoid bodies. Diploid forms were often seen, and, not infrequently, tetrads. The components of a pair were not always of equal size, and separation was not always complete. The number of the bodies in a single erythrocyte varied greatly, from one or two to 20 or more. Occasional bodies, seen in profile, seemed to lie on or immediately beneath the

[2] The most recent counts show a slight improvement in his anaemia. The intra-erythrocytic bodies, however, are still very numerous.

surface of the cells. Roughly 25 per cent. of the cells were affected. No free forms were noted. They were never found within leucocytes. In Giemsa and Wright stained smears from Case 3, many of the affected erythrocytes appeared to be depleted of haemoglobin save for a narrow rim at the periphery. The bodies, when present, were often concentrated at the margin of the cells. The bodies could be easily distinguished from the uniformly distributed granules of basophilic stippling, and from Jolly-Howell bodies which were quite abundant, or from overlying blood platelets.

A film of blood was fixed in methyl alcohol, Zenkerized, and stained overnight with Mallory's phospho-tungstic acid haematoxylin. The bodies were unstained, appearing as sharply outlined empty spaces against the bluish-lavender background of the cells. Some of the spaces were circular, others more elongated or rod-shaped. There was a slight concentration of the stained background about the bodies.

In fresh unstained blood suspensions on a warm stage, the bodies were quite easily seen. They were slightly more refractile than the surrounding red cell substance, and were completely colourless. They exhibited oscillatory motion independent of movements of the cell as a whole, and changed their relative position within the cell. The individual particles, however, showed no definite motility in dark field illumination.

When blood films were fixed in methyl alcohol, treated with solutions of 1 per cent. hydrochloric acid (3 parts) and 2 per cent. potassium ferrocyanide (1 part), and counterstained with basic fuchsin, the bodies gave a positive iron reaction. The identity of the siderous granules with the Giemsa stained bodies was proved by photographing individual cells, in a Giemsa stained slide, decolorizing with acid alcohol, restaining with hydrochloric acid potassium ferrocyanide, and again photographing the same cells.

The bodies did not retain the Gram stain. They failed to give a Feulgen reaction.

Heparinized blood from Case 3 was laked with distilled water, or with saponin, the centrifuged sediment washed and again centrifuged at about 2,500 r.p.m. Smears of the sediment, stained with Giemsa or for iron, showed an enormous concentration of the bodies, the appearance being that of a thick smear from a bacterial culture of some small coccoid organism (Plate 3, Fig. 9). The sediment was suspended in a solution of crystalline trypsin and incubated for 24 hours at 37° C. at pH 7·8. Neither the form nor the iron-staining of the bodies was altered by this procedure. The iron-staining and morphology of the bodies were not affected by exposure to N/20 hydrochloric acid. On the alkaline side, however, the iron-staining was lost at about pH 10·7, although the morphology of the bodies and the staining with Giemsa were not affected. The sedimented bodies were treated with a solution of sulphuretted hydrogen in 0·9 per cent. salt solution. They became brownish, and only an occasional body was blackened. Haemosiderin pigment under similar treatment is black. A blood film treated with 3 per cent. silver nitrate and exposed to light showed no blackening of the bodies.

Six and five-tenths c.c. of citrated blood was examined for ferritin by the method of Granick (1942) and no crystals were obtained with cadmium sulphate. We are indebted to Dr. E. Chargaff for carrying out this test. The sedimented bodies were not anisotropic when examined with the polarizing microscope.

An attempt to demonstrate the presence of alkaline phosphatase in the centrifuged concentrate of bodies by the Furth-Kabat stain was unsuccessful.

When a tube of heparinized blood from Case 3 was placed in a strong electromagnetic field, the iron-containing erythrocytes were drawn to the glass along the line of contact with the magnet; the unaffected erythrocytes settled to the bottom of the tube. A film prepared by pipetting the cells from the side of the tube showed a very striking concentration of the affected cells, most of which were ring forms with depleted haemoglobin. Suspension of the micro-organisms obtained from spleen culture did not migrate in the magnetic field. A suspension of the bodies in saline solution, obtained by centrifuging laked blood and washing the centrifuged sediment, was not agglutinated by patients' or control normal serum in 1 in 10 or 1 in 20 dilutions. An attempt was made to obtain complement fixation. The centrifuged laked blood, containing a rich suspension of the bodies, was formalinized, adjusted to pH 7·5 and used as antigen against the patients' serum. No fixation of complement was obtained.

Bodies in reticulo-endothelial cells. As has been mentioned in the autopsy records, minute coccoid bodies staining blue with Giemsa were seen in the lining endothelial cells of the splenic sinuses, in the Kupffer cells, in reticular cells of lymphnodes, and in large reticulo-endothelial cells of the marrow. They frequently occurred as diploid bodies, less often as tetrads. In the bone marrow of Case 2, the small bodies appeared to fuse into larger masses up to the size of a red cell. The staining with Giemsa was somewhat more bluish than the forms seen in the red cells. They gave a positive iron reaction. The haemosiderin present could be distinguished by its greater refractility and its failure to stain blue with Giemsa. In Gram stained sections, the bodies did not retain the gentian violet.

The question may be raised at this point whether the structures seen in or on the erythrocytes and those within the endothelial cells are identical. In Giemsa stained sections of the spleen, particularly from Case 2, and in smears of the bone marrow, there is a distinct difference in staining. The bodies in the erythrocytes take a reddish-purple or lavender colour, those within the endothelial cells or large mononuclears are bluish. This may be due to the fact that in the erythrocytes the background is red. In the pale staining cells of Case 2, they stained more blue than purple. Apart from this difference, the bodies resemble each other in size, form, and arrangement. In Giemsa preparations the staining varies from a deep blue to a somewhat greenish or brownish blue, in which case they seem somewhat more refractile. In general the smaller particles take a pure blue stain. The possibility that the bodies are some form of blood pigment cannot be excluded, although they

can readily be distinguished from the coarser brownish clumps of haemosiderin, which are found predominantly within or amongst the reticular cells of the pulp.

The possibility that the granules in the cytoplasm of the endothelial cells lining the splenic sinuses may be ingested platelets must be considered. In unstained Zenker-fixed sections, the bodies are colourless or very faintly brownish, not refractile, although they can be distinguished from the surrounding cytoplasm. They give no iron reaction, and are decolorized with Gram, staining red with safranin, basic fuchsin, or dilute carbol fuchsin counterstain.

Alrutz, Nortell, and Piette (1926) described and pictured similar structures in a case of thrombocytopenic purpura. We may quote from their article.

'The most interesting findings were discovered with the oil immersion. Within the cytoplasm of the endothelial cells of various sinuses, and also in the reticular cells of the glomeruli, numerous small irregular granules were found. They were stained deep blue with methylene azur and were practically invisible in haematoxylin eosin sections. The granules were, in our opinion, degenerated platelets, normally present in the spleen in much less number. Some better preserved platelets were also seen in the cytoplasm of endothelial cells. The picture of enormously increased phagocytosis of the platelets by the reticulo-endothelial cells of the spleen may help to explain the decrease of platelets in the blood stream and the associated haemorrhagic diathesis, and also the effect of splenectomy and subsequent increase of platelets.'

The identity of these bodies as described and pictured by Alrutz, Nortell, and Piette with those seen in our cases seems certain, but we cannot agree with their interpretation of them as degenerated phagocyted blood platelets. We have frequently seen ingested platelets in bone marrow smears; they conserve their normal structure and staining sufficiently to make identification easy; never do they take an intense blue stain. Moreover, the individual bodies are smaller than blood platelets and often show a definite arrangement in diploid form and even occasionally in short chains. Degenerated platelets in old thrombi stain reddish, not blue, with Giemsa; the granules of the platelets are not demonstrable in tissue sections stained by this method.

In order to obtain information as to the frequency with which such structures may be found within the sinus endothelium of the spleen and the particular conditions under which they occur, we have made a systematic study of sections of spleens removed at operation and spleens obtained from patients dying of various diseases on whom autopsy had been performed within four hours after death. The tissue was fixed in Zenker without acetic acid, sectioned at 4 micra, and stained overnight with buffered Giemsa solution. The presence or absence of the bodies was recorded without knowledge of the clinical diagnosis. The results of this study are shown in tabular form given on the next page.

From this it appears that the bodies occur in a high percentage of cases of thrombocytopenic purpura, in a smaller proportion of the cases labelled

Bodies in Sections of Spleen

Clinical diagnosis	Present	Absent	Doubtful
Thrombocytopenic purpura	24	5	3
Haemolytic jaundice	8	5	6
Banti's disease Cirrhosis of liver Congestive splenomegaly	4	16	2
Gaucher's disease	0	2	—
Leukaemia	0	4	—
Lymphosarcoma	0	4	—
Reticulo-endothelioma	0	1	—
Haemochromatosis	0	2	—
Giant follicular hyperplasia	0	1	—
Aleukaemic leukaemia?	0	1	—
Brucellosis?	0	1	—
Splenomegaly, unclassified	0	18	—
Miscellaneous autopsies, chiefly cases of secondary anaemia	0	19	—
Rheumatic fever	7	1	3

haemolytic jaundice or Banti syndrome, and in spleens removed from children with rheumatic fever. It may be of interest that three positive 'Banti' cases were in young people without cirrhosis of the liver. The bodies were absent in a variety of miscellaneous conditions examined as controls. Unfortunately there were not at our disposal blood smears from most of these cases, so that the question as to whether there is a correlation between the endothelial inclusions in the spleen and the occurrence of bodies in the circulating erythrocytes cannot be answered. However, we have examined a series of blood smears of various haematological conditions for the presence of the bodies, with the following results:

Bodies in Blood Smears

Clinical diagnosis	Present	Absent	Doubtful
Thrombocytopenic purpura	2	5	4
Haemolytic jaundice	4	7	5
Sickle cell anaemia	2	8	—
Osteosclerotic anaemia	—	4	—
Cooley's anaemia	—	7	—
Pernicious anaemia	—	11	—
Severe secondary anaemia	—	3	—
Aplastic anaemia	—	4	—
Gaucher's disease	—	2	—
Banti syndrome	—	1	—
Splenomegaly, origin undetermined	—	1	—
Malarial anaemia	—	1	—
Haemolytic anaemia with co-agglutinins	—	1	—

It is apparent that bodies of the type described are found, though inconstantly, in the circulating blood in much the same groups of cases in which they occur within the endothelium of the splenic sinuses, namely, patients with the thrombocytopenic purpuras and haemolytic jaundice. But even in the three splenectomized patients in whom they were fairly numerous, the percentage of affected red cells was not nearly so great as in the cases here reported. Often typical bodies were found only after looking over many fields. The three patients who showed them most abundantly had all had

their spleens removed. In one of them, a young girl with typical purpura, a smear taken two days before splenectomy was negative, whereas one obtained two days after the operation showed many typical bodies in each field. The spleen section in this case had many minute bodies of similar size, but with more bluish staining, in the endothelium of the splenic sinuses.

Cultural studies. No bacteriological studies were made of the spleens from Cases 1 and 2. From the spleen of Case 3, aspirated pulp was transplanted into Geiman's (1941) semi-solid and into Noguchi and Battistini's (1926) leptospira media. The latter was contaminated, and discarded. In the tubes of Geiman's media, after three days at 28 to 30° C., there was obtained an apparently pure growth of a small pleomorphic organism, which had the following characteristics. Short bacillary forms predominated, but there were also coccoid, and comma-shaped ones. Often there were polar granules, or a single granule. The ends of the rod were often tapering (Plate 3, Fig. 10). When first isolated, the organisms were Gram negative. In later transplants, the Gram staining was variable, but Gram positive forms were always most numerous. In Wright or Giemsa stained preparations, the granules stained a deep purplish-blue against the paler blue of the remainder of the organism. In dark field they were non-motile. The organisms grew readily in plain agar, forming discrete, small colonies, at first translucent, later more opaque and greyish. In plain nutrient broth they produced turbidity without pellicle formation. They failed to ferment glucose, lactose, sucrose, salicin, or mannite, and did not produce indol. No haemolysis was produced on blood-agar plates.

The organism isolated from the spleen did not agglutinate with serum of the patient, obtained after his spleen had been removed. When a suspension of the spleen culture was incubated with normal red cells, many of the small diploid or bacillary forms attached themselves to the surface of the erythrocytes and some appeared to lie within them. The appearance in Giemsa preparations was indistinguishable from that of the naturally occurring bodies (Plate 4, Fig. 11). They did not, however, give an iron reaction.

Repeated cultures from the blood of Case 3, on Geiman's semi-solid, Geiman's fluid medium, Noguchi leptospira medium, and in plain broth, remained sterile, except for one culture (November 22, 1943) which yielded an organism which somewhat resembled that from the spleen, but was consistently bacillary, produced a yellowish coloration on agar plate colonies, and had a pungent odour. Although it was not positively identified, it was regarded as a contaminant, and not further investigated.

Animal inoculations. 1. After a preliminary observation period of four days, 1 c.c. of washed saline suspension of a 48-hour culture in Geiman's fluid medium from the spleen of Case 3 was injected intravenously into a *Macacus rhesus* monkey. This was not followed by any evidence of illness; the temperature remained within normal limits, and repeated blood smears and cultures were negative. At the same time, 0·5 c.c. was injected intracutaneously and subcutaneously above the orbit. No verruca or other

inflammatory reaction was produced. On December 4, 16 days after injection, splenectomy was performed. Histological examination of the spleen (Zenker and Regaud fixation, Giemsa stain) showed a few diploid and short bacillary bodies within sinusoids or amongst reticular cells of pulp. There had been no multiplication and no pathological changes were present in the spleen. After the operation there were no noticeable symptoms. No parasites appeared in the blood, and complete weekly blood counts showed no significant deviation from normal. Several blood cultures proved sterile. On the seventeenth day after splenectomy the same monkey was injected with 2 c.c. of citrated blood from Case 3, which on this day contained very numerous intra-erythrocytic bodies. The results were again negative. This experiment was discontinued after three weeks' further observation.

2. A rabbit was splenectomized under ether on November 16. No parasites appeared in the peripheral blood. On November 24 the animal was injected intravenously with 0·5 c.c. of a saline suspension of a 48-hour transplant of the spleen culture from Case 3. Blood films were examined daily, and were negative. The animal died on December 15 from a superficial wound infection, spreading to the abdominal and thoracic wall.

3. Two splenectomized male guinea-pigs were injected intraperitoneally on November 24, 1943, with 1·0 c.c. of a saline suspension of a 48-hour transplant from spleen culture of Case 3. Guinea-pig B_1, on the second day, showed a few suspicious coccoid bodies in the erythrocytes. They were not found on subsequent examinations. The animal was killed on November 29. No significant changes were found in tissues. Blood culture yielded a growth of pneumococci. Guinea-pig B_1 died from lobar pneumonia 15 days after injection. No parasites were found in the red cells in daily smears.

Two splenectomized male guinea-pigs were inoculated intraperitoneally seven days after the operation with 0·75 c.c. of citrated fresh blood from Case 3. Results were negative. There was no Mooser reaction.

4. Four old and young rats of a Bartonella-free strain provided by Miss Naiman of the Department of Bacteriology were splenectomized on November 30. Daily blood examinations failed to show parasites. On December 12 two were injected with 0·2 c.c. of splenic culture subcutaneously, two others with 0·5 c.c. intraperitoneally. No bodies appeared in the blood. After nine days they were injected with blood from Case 3, again with negative results.

5. Four splenectomized white mice were injected five days after the operation with citrated blood from Case 3. All proved to be infected with *Eperythrozoon coccoides*, but no bodies resembling those in the human cases were detected.

6. Two hamsters were splenectomized on April 4, 1944. Repeated blood smears before and after operation showed no intra-erythrocytic parasites. On May 2, 1944, they were each injected intraperitoneally with 1 c.c. of defibrinated blood from Case 3, containing large numbers of the bodies. The animals showed no symptoms and daily examination of blood films disclosed no intracorpuscular bodies.

The animal inoculations thus yielded no additional information. The cultures obtained from the spleen proved to be non-pathogenic for the animals tested, nor was it possible to transmit the human disease by injection of whole blood.

Egg inoculations. Dr. Harry Rose and Miss Eleanor Molloy of the Department of Medicine have collaborated in this phase of our studies. Ground blood-clot and sterile citrated blood from Case 3 were obtained on several occasions and were inoculated into the chorio-allantoic membranes and into the yolk sac. Smears and Zenker-fixed 5-micra paraffin sections were studied. Eggs of different ages were injected, and examined at different intervals. Sections were stained with Giemsa. Purplish blue granules were found within the yolk cells, sometimes in enormous numbers. They were situated either in the protoplasmic walls of the cells or in the cytoplasmic processes projecting from them. Often they were arranged in colony-like clusters. Their size varied from a fraction of a micron to two or three micra; the majority fell within the range of the bodies seen in the inoculated red blood corpuscles. They gave no iron reaction. The accompanying photomicrograph shows the resemblance of these granules in form and distribution to the elementary bodies of lymphogranuloma venereum and similar viruses (Plate 4, Fig. 12). Unfortunately, eggs inoculated with control normal blood and even uninoculated eggs (Plate 4, Fig. 13) showed identical granules. The significance of these bodies remains to be determined, but it is obvious that they bear no relation to the intra-erythrocytic bodies found in the blood of our patients, and that no conclusions can be drawn from these experiments.

Discussion

What can be said of the nature of these bodies? There are three possibilities to be considered: that they are artefacts, that they are parasites, or that they represent some unknown precursor or breakdown product of haemoglobin. It is necessary to discuss each of these possibilities in some detail.

That they represent artefacts arising during fixation or staining can be immediately ruled out by the fact that they are readily visible in unstained fresh preparations. Furthermore, they can be demonstrated by various staining techniques, and they give a positive iron reaction.

That the bodies are parasites. When they were first observed, this seemed an attractive and likely interpretation. The resemblance of the clinical course of these patients to that of the febrile phase of Carrion's disease seems to point to a similar, if not identical, parasitic agent. The pathological changes in the two fatal cases were not inconsistent with those which have been found in patients dying during the anaemic phase of Oroya fever (Strong, Tyzzer, Sellards, Brues, and Gastiaburu, 1915). Moreover, as will be pointed out, although there are differences in staining and morphology between the *B. bacilliformis* and the bodies described, there are also resemblances sufficiently close to justify discussion as to their possible relationship to this or

similar blood parasites. Plate 1, Figs. 3*a*, *b*, *c*, and *d*, which are objective drawings representing the bodies found in these four cases, compared with *B. bacilliformis* (Plate 1, Fig. 3*e*) and *Haemobartonella muris* (Plate 1, Fig. 3*f*), offer convincing evidence of their general resemblance. None the less, on further study it has not been possible to identify this organism with any of the known parasites of man or animals. The four known genera of non-protozoal organisms which parasitize in or upon the erythrocytes of man or animals are: *Bartonella, Haemobartonella, Grahamella, and Eperythrozoa.* There are reasons for excluding our bodies from each of these genera.

Bartonella. The only known species of this genus is the *Bartonella bacilliformis,* the causative agent of Carrion's disease (Oroya fever, Verruga peruana). Although the clinical history of the fatal cases here reported closely resembles that of the anaemic phase of Oroya fever, epidemiological considerations, the absence of an eruptive phase, as well as morphological and cultural differences, make it highly improbable that the organism in question is identical with *Bartonella bacilliformis.* Carrion's disease has not been reported outside of Peru, Colombia, Chile, and Ecuador; none of these patients had been in South America. The only proven insect vectors are two species of *Phlebotomus,* neither of which occurs in New York or New Jersey. None of the patients had shown a verrucous phase. Comparing the morphology of the bodies, we find striking differences. *B. bacilliformis* is more slender, rod-like forms are more numerous, and staining is reddish rather than purplish blue (Plate 1, Fig. 3*e*, and Plate 5, Fig. 14). Both are pleomorphic, and individual forms can be found which are indistinguishable. More important than morphological and tinctorial differences is the fact that the bodies under discussion, as they occur in or upon the erythrocytes, contain stainable iron. This unique property differentiates them therefore from the *B. bacilliformis,* which, when similarly treated, does not give a Prussian blue reaction (personal observation). There are also cultural differences between the organism obtained from spleen of Case 3 and cultures of *B. bacilliformis.* Growth on Geiman's semi-solid medium is somewhat more vigorous than that of *B. bacilliformis* and reaches the surface of the medium. The organism obtained from the spleen also grows in ordinary media and is, though not constantly, Gram positive. There is, however, no sharp distinction in the morphology of the cultural forms (Plate 3, Fig. 10) although the *B. bacilliformis* appears to be somewhat more slender (Plate 5, Fig. 15). Implicit in the definition of the genus *Bartonella,* as set forth by Tyzzer (1942) and Weinman (in press), is the multiplication of the organism within endothelial cells of the tissues. Although we found in the study of our fatal cases that bodies closely resembling those in the peripheral erythrocytes occurred also within endothelial and reticular cells in spleen, bone marrow, lymphnodes, and liver, there was little to suggest that they were undergoing active multiplication; and large cells stuffed with parasites, such as have been found in fatal cases of Oroya fever, and in the verruga nodules, were not seen in our cases. Another differential point is that the bodies appeared in the peripheral

blood after splenectomy, whereas the *Bartonella bacilliformis* is found in subjects whose spleen has not been removed.

Haemobartonella. Although some 21 more or less completely described species are known to occur in a variety of laboratory and wild animals (Weinman, in press), infection of man with *Haemobartonella* has not been reported. The features which characterize the genus *Haemobartonella* are as follows. Pleomorphism; coccoid forms, diploids, rods or batonnets, occasional ring forms, and even branching filaments, have been found in one or other species. Only red blood corpuscles are parasitized; no intrahistiocytic or endothelial multiplication has been observed. In almost all cases removal of the spleen initiates the appearance of the organisms in the peripheral blood, and brings about a transient or fatal anaemia. Successful cultivation has been reported for a few species, but in general has proved difficult. Transfer to closely related hosts, after previous splenectomy, has been successful in some instances. In some respects the bodies here described conform to these criteria; in others they do not. The morphology and staining are sufficiently like many of the described forms of *Haemobartonella* to prevent their exclusion on that basis (Plate 1, Fig. 3*f*, Plate 5, Fig. 16). The occurrence within reticulo-endothelial cells, even if there is no convincing evidence of an intracellular multiplication phase, has not been seen in infections with *Haemobartonella*. The effect of splenectomy in favouring their appearance in the peripheral blood is characteristic both of the bodies here reported and of the *Haemobartonella* infections of animals. In the cultures obtained from the spleen of Case 3 growth was vigorous and rapid; the difficulty of cultivating *Haemobartonella* on artificial media has been mentioned. We have seen no reference in the literature to possible iron-staining of *Haemobartonella*. *Haemobartonella muris* does not give a positive iron reaction with hydrochloric acid and potassium ferrocyanide (personal observation). Another differential point is that in our patients anaemia preceded the removal of the spleen; animals infected with *Haemobartonella* became anaemic only after the spleen has been ablated.

Grahamella. These are characterized, to quote Tyzzer (1942), 'by a marked degree of uniformity—appearing as rods with only an occasional rounded form, and are situated definitely within the red blood cells. They are not greatly increased by splenectomy, infect only a small percentage of the red cells, are not known to be pathogenic, are not eradicated by treatment with arsphenamine (as are the *Haemobartonella*) and are readily grown on certain media.' It is obvious, with further analysis, that our bodies do not meet these criteria, and should not be classified under this genus.

Eperythrozoa. These are blood parasites similar to *Bartonella* and *Haemobartonella* in many particulars, causing diseases in which anaemia is a prominent symptom. They are characteristically round with numerous annular and disk-shaped elements; rod forms are short and unbranched and on the surface of the red cells, and rods are rare and not disposed in chain formation. They occur both on the cells and free in the plasma. Infection may produce

symptoms, even in animals with intact spleens, but splenectomy renders a latent infection active. No developmental phase is known to occur in tissue cells, although the organisms may be found within phagocytic cells. Successful cultivation has not been reported. The type species, *Eperythrozoon coccoides* (Schilling, 1928) is a common parasite of the white mouse, and it has been found in six other species. It is transmitted by the mouse louse, *Polyplax serratus* (Neitz, 1927; Neitz, Alexander, and Du Toit, 1934). Infection of sheep with the *Eperythrozoon ovis* has been reported from South Africa, Algeria, Iran, and France. The clinical course of intense anaemia accompanied by irregular fever and sometimes jaundice, all intensified by splenectomy, presents certain analogies to that of the human cases here reported. The question as to whether the bodies in our cases may be classed as a new species of *Eperythrozoon* cannot be dismissed without discussion. Morphological considerations alone are probably not decisive. Free forms were only exceptionally found in our preparations, and may have been due to mechanical dislodgement of the parasites from the cells. The *Eperythrozoon* characteristically occur free in the plasma, as well as attached to erythrocytes, and this would seem to be a significant distinction. Annular forms were seen very rarely in our preparations, whereas they are in general typical of the various species of *Eperythrozoa*, although these too may be very pleomorphic, assuming ovoid, comma, dumb-bell, and rod forms. Since culture on artificial media has not been reported, and since detailed histopathological studies of infected animals appear not to have been carried out, it is difficult to reach any conclusion as to the possible relationship of our bodies with one or other members of this genus. In this connexion it is interesting that Schüffner (1929) found bodies closely resembling the *Eperythrozoa coccoides* of mice in the blood smear of a child with symptoms resembling von Jaksch's anaemia. The photomicrographs appended to his paper show numerous free discoid or annular forms in the plasma, and it is obvious at a glance that these structures bear little resemblance to those in our cases.

We have also compared the bodies with *Anaplasma marginale* of cattle. Although there is a resemblance in size and staining, they differ sharply in several respects. The red cells rarely contain more than three or four *Anaplasma*, whereas as many as 20 bodies may be present in a single erythrocyte in our cases. *Anaplasma* is not associated with dehaemoglobinization of the cells. *Anaplasma* gives no iron reaction with hydrochloric acid and ferrocyanide. Diploid and tetrad forms are rarely, if ever, seen. It seems that these distinctions rule out a possible relationship between the inclusions found in our cases and those found in anaplasmosis.

To sum up, it seems inadvisable at present to classify our bodies under any of the existing genera of non-protozoal blood parasites. A general morphological resemblance to the *Bartonella*, the *Haemobartonella*, and perhaps also the *Eperythrozoa*, is not to be denied, but there appear to be differential features which are sufficient to exclude them from each of these genera. Their siderophilic character alone would distinguish them from *Bartonella*

and *Haemobartonella*. So far as we can ascertain, iron-staining has not been applied to the *Eperythrozoa* or *Grahamella*.

Common as is infection with *Haemobartonella* in many species of mammals, we have found but two references to the occurrence of *Bartonella*-like bodies in human blood in diseases other than in Oroya fever or Carrion's disease. Edelman in 1927 demonstrated at a meeting of the *Gesellschaft der Aerzte* in Vienna blood slides from a case of thrombocytopenic purpura without splenectomy, in which inclusions closely resembling the *Bartonella* of Oroya fever were present. This presentation seems to have aroused little interest, and we have found no complete report of his observations.

Giordano and Blum (1937), in their paper on acute haemolytic anaemia (Lederer type), called attention to the similarity of the clinical picture in this disease with that of the febrile anaemic phase of Oroya fever, and suggested that in future studies and observations in Lederer's anaemia the blood smears should be carefully examined for possible bacteria-like inclusion bodies within the red blood cells. The authors themselves do not appear to have seen such bodies in their cases.

Our attention has been called to a recent paper by Otto and Rezek (1943). These authors reported the case of a man of 45 years with intractable anaemia not responding to iron, repeated transfusions, or splenectomy. Pleomorphic bodies were found in great numbers in the erythrocytes. So far as can be judged from their description and illustrations, these are identical with those in our cases. They were greatly increased in numbers after removal of the spleen. Attempts at cultivation and animal inoculation made by Dr. Koppisch with citrated blood sent from Miami to the School of Tropical Medicine in Puerto Rico yielded no additional information. The *Bartonella*-like nature of the blood parasites could thus be surmised only from their morphology in blood films. On this basis they concluded that the 'inclusion bodies' were most comparable to *Bartonella canis* (Kikuth), and suggested the possibility of this organism being pathogenic for man. Dr. Rezek has kindly allowed us to study his preparations. The bodies in the blood films appear less numerous than in our cases, but have a similar staining and morphology. They give a positive iron reaction.

That the bodies are not parasitic, but represent an iron-containing component (not haemosiderin) derived from the breakdown of haemoglobin or a precursor of haemoglobin. It is pertinent to discuss in this connexion the relationship of these iron-reacting bodies to the so-called siderocytes described by Grüneberg (1941, 1943). This author found in the blood of normal rats, mice, and human embryos, erythrocytes which, in addition to haemoglobin, contained some free or easily detachable iron, probably belonging to a hitherto unidentified precursor of haemoglobin. These cells, called siderocytes, showed distinct siderotic granules, sometimes a dozen or more per cell. Normally they occurred only in the embryo or new-born, but they were present also in adult mice which had recovered from the anaemia associated with the recessive gene for flexed tail and belly spot. A paper by Doniach, Grüneberg, and

Pearson (1943) records the occurrence of similar siderocytes in seven adult human patients. Five of these had been splenectomized for the following clinical conditions: Banti syndrome, thrombocytopenic purpura, traumatic rupture of spleen (two cases), and splenic anaemia. Two cases had not been splenectomized: one of severe anaemia associated with renal rickets, another of malignant hypertension with renal insufficiency. The bodies depicted by the authors are in the form of granules or small spherules of varying size. No mention is made of rod forms, nor of their staining in Wright or Giemsa preparations.

Through the courtesy of Professor Leslie Dunn we have been able to examine blood films from new-born mice of the strain showing the genetic abnormality described by Grüneberg. In conformity with his observations we have found that about 80 per cent. of the erythrocytes contain siderophilic granules. These stain blue, without any purplish component, in Giemsa preparations; they are extremely numerous, and very variable in size and shape, ranging from irregular clumps to fine punctate stippling. Occasionally they may be found in pairs or short chains, but in general they have a totally irregular distribution (Plate 1, Fig. 3*g*, Plate 5, Fig. 17). In contrast, the structures in our cases have a sharper outline, stain more intensely and with a more purplish cast, they are less numerous, and their occurrence in diploid forms is very frequent. Although individual granules or rod-like bodies can be found which are indistinguishable from the siderophil granules of mouse blood, it is not certain that these two types of structure are identical.

Case (1943) in a recent report found siderocytes in 'large numbers in stored blood of cats, dogs, and human beings'. He believes that all red cells go through a phase as a siderocyte, and then the granules are extruded from the cells, a process which is attended by a fall in total blood pigment of between two and seven per cent., and a corresponding increase in non-haemoglobin plasma-iron and a bilirubin-like substance. The change is affected by availability of oxygen, inhibited by storage at low temperatures, and accelerated by heat and chemical agents. After extrusion of the siderophil granules, the erythrocytes become susceptible to phagocytosis. It is concluded that the siderocyte is not essentially a young cell, that it is probably the stage before the cell is removed from the circulation, that it probably appears in the blood of all animals, that the iron is katabolic, and that it is closely related to, if not identical with, the easily split blood-iron studied by Lemberg, Legge, and Lockwood (1939).

A blood slide from Case 3 was mailed to Dr. Case of the University of Birmingham. He has very kindly sent us the following comment: 'I cannot convince myself that the structures shown are identical with the siderotic granules, but by applying the iron stain over your Giemsa, I can confirm your statement that many siderocytes are present, but your granules are not identical with the siderotic granules, although they often occur in the same cells. There are thus two theories tenable: (1) that your suggestion of a parasite is valid, and that the cells affected are showing the siderotic change,

as damaged cells do; (2) that your granules represent some other fraction of the haemoglobin degradation. If this is so, it would seem to be an aberrant phenomenon, as I cannot demonstrate it in films of my own which have just been stained for the purpose.' Dr. Case also writes that 'I have not satisfied myself that it is possible to demonstrate the granules with Giemsa or Romanowsky stain, and such a procedure would not be certain'. However, in our experience, the siderotic granules in the new-born mouse are readily stained with Wright or Giemsa.

Since a detailed account of these interesting studies is not yet available, their bearing upon the cases here reported is not clear. Should it prove true that all red cells normally pass through a siderocyte phase before destruction, it remains to be disclosed why such cells do not normally appear in the circulating blood and why, in certain cases of anaemia, they should be present in such numbers.

The morphology of the bodies in blood smears stained with Wright or Giemsa, though not in all respects identical with that of known erythrozoan parasites, nevertheless is very suggestive, and experienced observers who have seen these preparations have so interpreted them. The very frequent occurrence of diploid and tetrad forms implies division within the cells and is a point in favour of their parasitic nature. On the other hand, the specific iron-staining of the structures is a feature which has never been noted, if indeed it has been looked for, in any of the erythrocytic parasites. One would have to postulate that if these are micro-organisms, they have the unique property of absorbing or incorporating iron from the breakdown of haemoglobin.

The morphology of the micro-organisms isolated from the spleen of Case 3 closely resembled that of the bodies in the red cells. Since, however, the organisms were not siderophilic, failed to agglutinate with the patient's serum, and proved to be non-pathogenic for laboratory animals, it was impossible to identify them with the intra-erythrocytic bodies or to ascribe to them any aetiological importance. Failure to reproduce the disease in animals by injection of whole blood into laboratory animals does not exclude the possibility that the structures within the red cells are parasitic, or that the anaemia is of infectious nature. But it is obvious that positive support for such a theory is lacking.

Whether the bodies in these cases are identical with the siderophil granules of Grüneberg and Case is difficult to decide; should they be so interpreted, their appearance in large numbers in the peripheral blood in certain cases of anaemia is still of great interest, and demands further investigation.

Summary

1. Three cases of severe anaemia are reported, in which, after splenectomy, the erythrocytes contained iron-staining coccoid or bacillary inclusions.

2. Although morphological characteristics suggest a relationship to certain

intra-erythrocytic parasites, no conclusive proof of their parasitic nature has been obtained.

3. An alternative interpretation, namely, that they are identical with the iron-containing bodies described by Grüneberg, is discussed.

We desire to express our thanks to the following scientists who have, in one way or another, assisted us in our study: Col. Richard P. Strong, Prof. Ernest Tyzzer, and Prof. S. B. Wolbach for reviewing our preparations; to Dr. David Weinman for allowing us to study his unpublished monograph on *Bartonella*, and for giving us slides and cultures of *B. bacilliformis* for comparison; to Dr. Michael Heidelberger for performing complement fixation tests and for the use of his electromagnet; to Dr. Erwin Chargaff for chemical determination to ascertain whether the iron-reacting bodies were identical with ferritin; to Prof. Leslie Dunn for supplying us with a strain of curly tailed mice, and to Miss Naiman, of the Department of Bacteriology, for a strain of *Bartonella*-free rats; to Miss Eleanor Molloy for co-operation in egg inoculations; to Dr. H. Rosenthal for sending us blood films of the child of Case 1, and to Dr. P. Rezek for preparations from his case; to Dr. G. Dikmans, of the U.S. Department of Agriculture, for slides of *Anaplasma marginale*; and to Drs. Allan O. Whipple and Elliott for performing splenectomy upon a monkey preparatory to inoculation.

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FIG. 3 a. Case 1. Blood smear. Drawing. Wright stain. ×865.

FIG. 3 b. Child of Case 1. Blood smear. Drawing. Wright stain. ×865.

FIG. 3 c. Case 2. Blood smear. Drawing. Wright stain. ×865.

FIG. 3 d. Case 3. Blood smear. Drawing. Giemsa stain. ×865.

FIG. 3 e. *Bartonella bacilliformis*. Drawing. Giemsa. ×865.

FIG. 3 f. *Haemobartonella muris*. Drawing. Giemsa. ×865.

FIG. 3 g. Newborn 'curly-tailed' mouse. Siderocytes. Drawing. Giemsa. ×865.

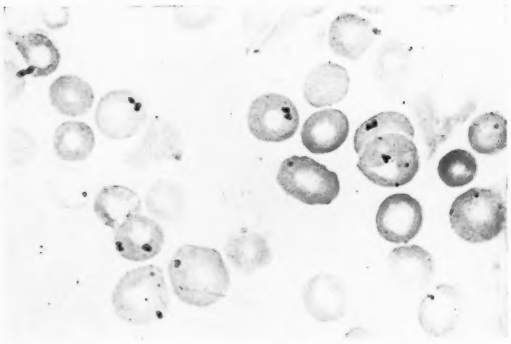

FIG. 4. Case 1. Blood smear. Wright stain. ×1037.

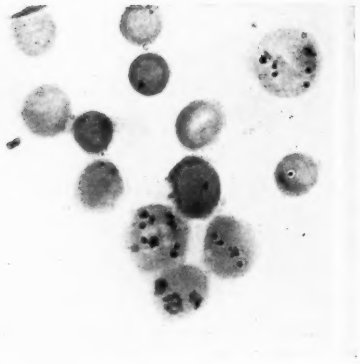

FIG. 5. Case 2. Blood smear. Wright stain. ×1015.

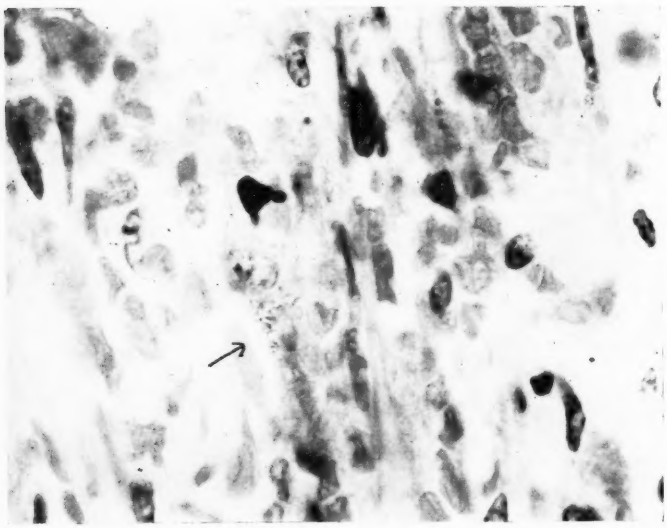

FIG. 6. Case 2. Accessory spleen. Sinus endothelial cell containing small cytoplasmic bodies. Giemsa. ×1050.

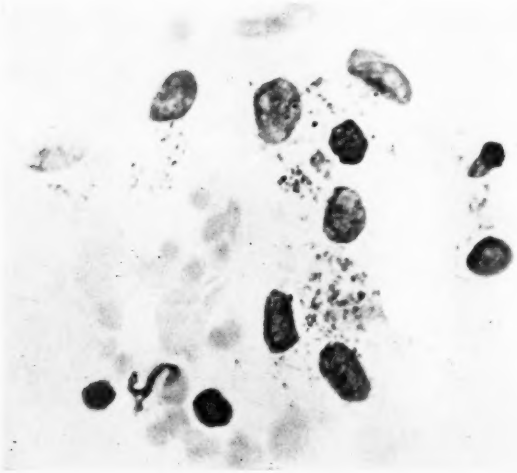

FIG. 7. Case 2. Large histiocytic cell in bone-marrow, containing numerous siderous cytoplasmic bodies. Giemsa. ×1050.

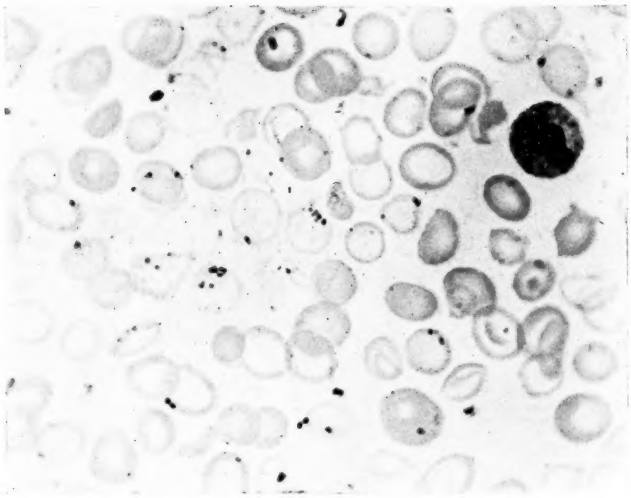

FIG. 8. Case 3. Blood smear. Giemsa stain. ×1050.

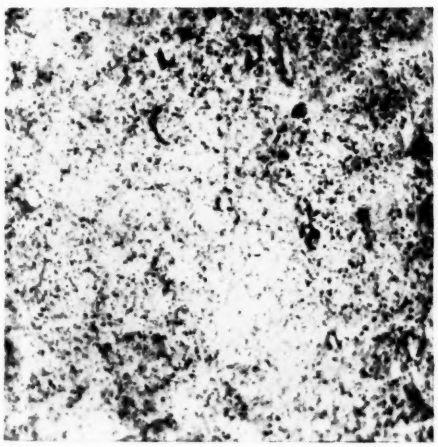

FIG. 9. Case 3. Laked blood, centrifuged sediment, stained with HCl-potassium ferrocyanide. ×1020.

FIG. 10. Case 3. Culture from spleen. First transplant to blood-agar. Giemsa. ×1050.

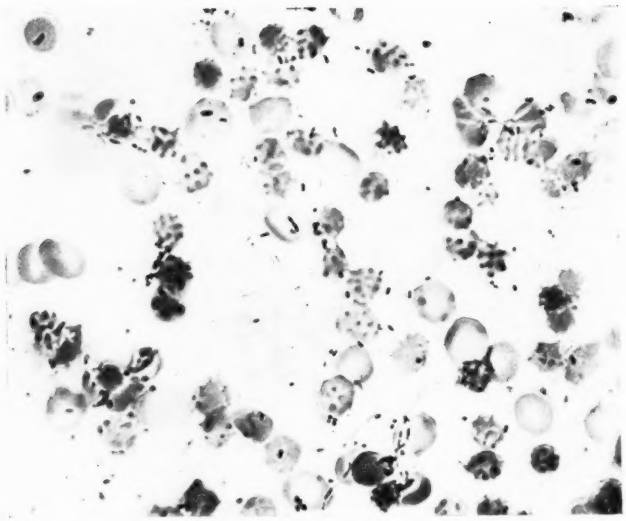

FIG. 11. Case 3. Culture from spleen suspended with normal red cells at 30° C. for 40 hours. Giemsa. ×1050.

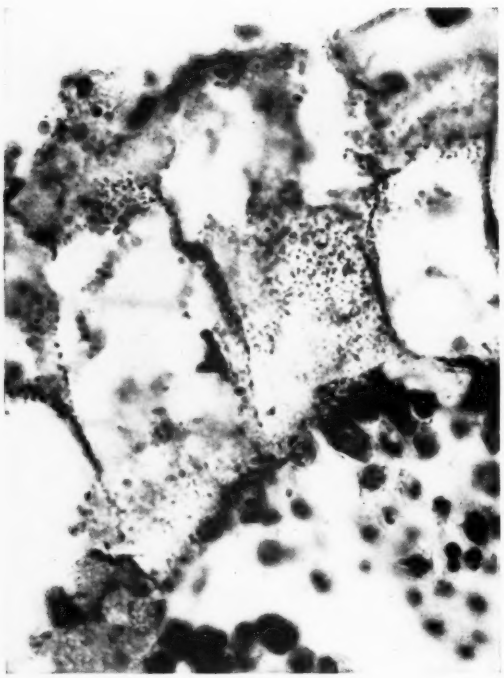

FIG. 12. Yolk-sac from egg inoculated with citrated blood from Case 3. Granules resembling 'elementary bodies' in yolk cells. Paraffin section. Zenker fixation, Giemsa stain. ×1050.

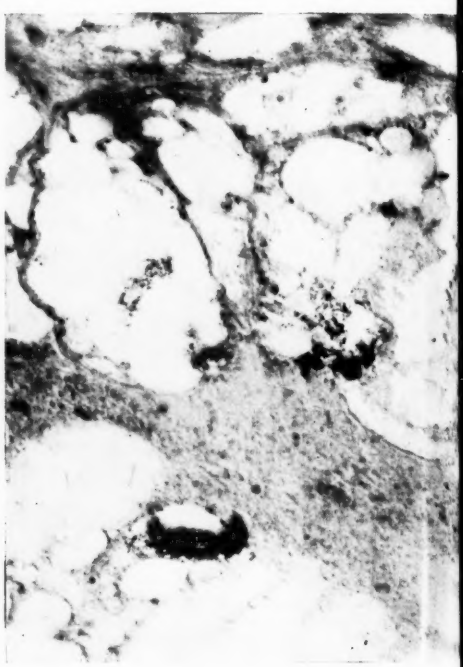

FIG. 13. Section of normal, uninoculated yolk-sac. Granules in yolk cells. Giemsa. ×1050.

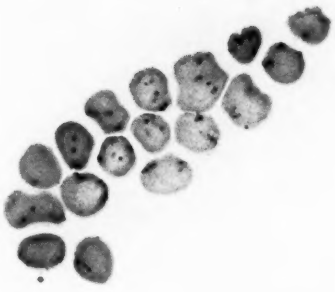

FIG. 14. *Bartonella bacilliformis* in blood of Oroya Fever. Giemsa. ×1050.

FIG. 15. *Bartonella bacilliformis.* Culture on Noguchi medium.

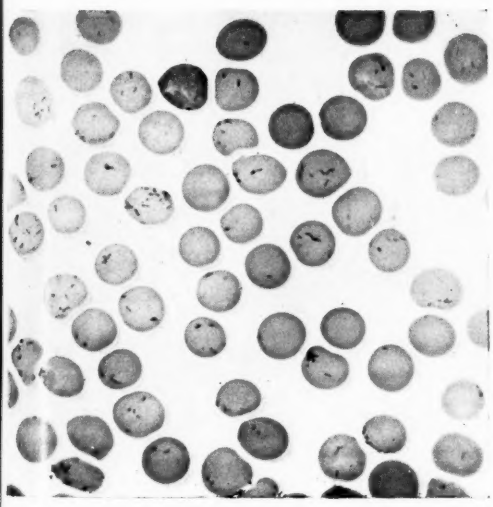

FIG. 16. *Haemobartonella muris.* Giemsa. ×1050.

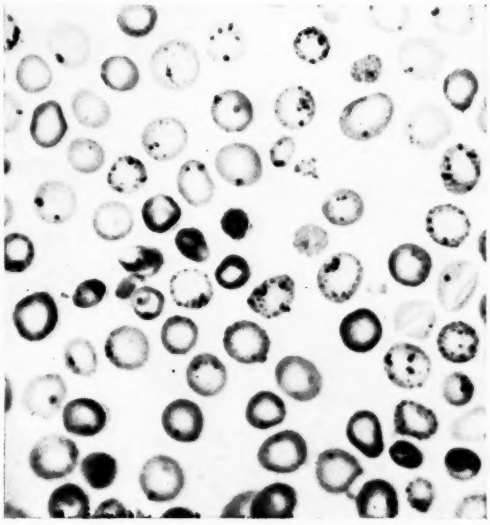

FIG. 17. Newborn 'curly-tailed' mouse. Siderocytes. Giemsa. ×1050.

616.151.5

CONGENITAL AFIBRINOGENAEMIA

REPORT OF A CASE WITH A REVIEW OF THE LITERATURE[1]

By J. L. HENDERSON, G. M. M. DONALDSON, and HAROLD SCARBOROUGH

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A TOTAL lack of fibrinogen in the blood-plasma is a rare occurrence. It may be either congenital or acquired; when acquired it is sometimes only transitory. Congenital afibrinogenaemia, which was first described by Rabe and Salomon (1920), should always be remembered as a possible cause of the haemorrhage in congenital 'bleeders'. There is still too great a tendency to regard congenital 'bleeders' of the male sex as haemophiliacs, without adequate clinical and laboratory investigations having been made to eliminate other possible causes of the haemorrhagic diathesis. A case of congenital afibrinogenaemia in an otherwise healthy boy of 11 years is reported in the present paper, and illustrates this tendency. Only six other cases of this disease have been recorded in the literature, but it seems probable that complete investigation of all congenital 'bleeders' would reveal more cases.

Case Report

J. L., Male, aged 11 years (born 4.9.1933).

History. The patient was born prematurely after the mother had twice threatened to miscarry. The birth was spontaneous. The birth weight was 5½ lb. Bleeding from the umbilicus began on the third day of life, oozing continued intermittently in spite of treatment with styptics, cautery, and ligature, and the baby was admitted to the Royal Edinburgh Hospital for Sick Children when 15 days old. Haemorrhage had not occurred from any other site. On admission, blood continued to ooze from the umbilicus and there was severe anaemia. A transfusion of 70 c.c. of the father's blood soon controlled the bleeding and greatly improved the infant's condition.

The boy has been admitted to hospital for persistent haemorrhage on 11 occasions to date. The reasons for admission are given in the following summary:

Epistaxis—six times (knock 4, nose blowing 1, nose picking 1).

Bitten tongue—once.

Shedding milk teeth—twice (associated once with bleeding laceration on knee and once with large haematoma over jaw).

Ulcerated lips—once (during measles).

Extraction of carious teeth—once.

[1] Received January 19, 1945.

The haemorrhage was arrested by transfusion on six occasions and subsided spontaneously on the other five. The boy sometimes suffered from slight shock after severe haemorrhage. Less severe degrees of haemorrhage not necessitating admission to hospital occurred on many occasions; the nose was the commonest site. Eruption of the first milk tooth caused severe haemorrhage and casting of the milk teeth was often associated with haemorrhage for two or three days. Extensive bruising has always been easily produced. The umbilical haemorrhage which began on the third day of life was diagnosed as haemorrhagic disease of the new-born. A diagnosis of haemophilia was made on the occasion of each subsequent admission to hospital until the eighth occasion, at the age of seven and a half years, when an absence of fibrinogen was discovered.

At the age of 10 years and nine months the right lower milk canine became loose as the permanent tooth erupted beside it, and intermittent oozing occurred. This lasted for several weeks, so it was decided to extract the milk canine and also the adjoining milk molar which was carious. He was admitted to hospital on 23.5.1944 for this to be done. Since fibrinogen was known to be absent from the plasma, it was expected that the extraction would be followed by prolonged bleeding, and arrangements were accordingly made for giving a continuous drip transfusion of plasma of known fibrinogen content. Apart from arresting the haemorrhage it was hoped that this procedure would yield information upon the total amount of fibrinogen required to stop bleeding and on the level of the fibrinogen in the patient's plasma at the time when bleeding ceased. It was decided not to set up the plasma drip until the day after extraction, and, in the interval, to employ local styptics which, it was expected, would prove ineffective. However, contrary to expectations all bleeding from the tooth sockets ceased two hours after extraction of the teeth and did not recur. The blood was still incoagulable, the capillary resistance unduly low, and the platelet count within normal limits (398,000 per c.mm.). The snake venom reaction was negative. The boy was having 500 mg. of ascorbic acid daily at the time, and viper venom and 'haemoplastic serum' had been applied locally for 15 and 10 min. respectively.

Examination. (1.6.1943.) Age nine years and nine months. The patient was a well-developed, very well-nourished, and healthy looking boy. Large ecchymoses were present in the skin of the calves of both legs and behind the right knee. Abnormal features were confined to the haemopoietic and vascular systems. The principal investigations carried out in haemorrhagic states on this and other occasions are given in tabular form for comparative purposes (Table I). The results of other blood investigations were as follows:

Erythrocytes	4,830,000 per c.mm.
Colour index	1·00
Reticulocytes	<1 per cent.
Packed cell volume	48·5 „ „
Mean cell volume	88 c.μ.
Leucocytes	9,200 per c.mm.
Differential count:	
Polymorphs	60 per cent.
Lymphocytes	35 „ „
Monocytes	4 „ „
Eosinophils	1 „ „

Re-examination. (26.10.1943.) Age 10 years and two months. Epistaxis had subsided spontaneously on the morning of admission to hospital

(26.10.1943) after persisting for several days. There was a severe degree of anaemia. The investigations pertaining to the haemorrhagic diathesis were again repeated (Table I). The results of other blood investigations were as follows:

Erythrocytes . . .	2,610,000 per c.mm.
Colour index . . .	0·77
Reticulocytes . . .	5·6 per cent.
Leucocytes	8,800 per c.mm.

Family history. The parents are first cousins. They are not aware of any bleeding tendency in either antecedent or collateral relatives. Both are 37 years of age and have enjoyed good health with no history of bleeding or abnormal bruising. The mother has not had any miscarriages. Father's plasma-fibrinogen 0·44 gm. per cent. Mother's plasma-fibrinogen 0·62 gm. per cent.

First child. Male, aged 14 years. Good health. No history of bleeding or abnormal bruising. Plasma-fibrinogen 0·30 gm. per cent.

Second child. Male, aged 11 years. (The patient.) Plasma-fibrinogen nil.

Third child. Female, aged six years. Good health. No history of bleeding or abnormal bruising. Plasma-fibrinogen 0·32 gm. per cent.

Fourth child. Female. Died of umbilical haemorrhage, aged six days. Birth spontaneous, weight about 7 lb. Umbilical haemorrhage began the day after birth, and the binder and napkin soon became soaked with blood. The bleeding apparently subsided, but a severe exacerbation occurred on the third day and the infant was admitted to the Royal Edinburgh Hospital for Sick Children on the same day. The general condition was fairly good on admission, but there was severe anaemia, the haemogloblin being 34 per cent. (Sahli). The umbilical bleeding had ceased. There was no jaundice. The infant was given 0·5 c.c. of synthetic vitamin K (Kapilon) intramuscularly. No further haemorrhage occurred and the infant was discharged two days later. In the early hours of the following morning severe umbilical bleeding recurred and the infant died in three-quarters of an hour. Unfortunately the plasma-fibrinogen, clotting time, and bleeding time were not estimated.

Clinical Features

The principal clinical features of congenital afibrinogenaemia in each of the seven published cases, including that recorded here, are shown in Table II.

Sex incidence. The disease affects both sexes. Five of the seven reported cases have been in boys, but no significance can be attached to this apparent predominance in males from such a small number of cases.

Haemorrhagic tendency from birth. The congenital nature of the haemorrhagic diathesis was shown in every case by the appearance of bleeding and ease of bruising in the early days of life.

Consanguinity. This is a common and highly significant feature. The parents were first cousins in three of the seven cases.

Heredity. The occurrence of a haemorrhagic diathesis in relatives was noted in two of the cases. The patients of Macfarlane (1938) and ourselves, both boys, each had a sister with a haemorrhagic diathesis. The parents were first cousins in both instances.

Fibrinogen. No fibrinogen could be detected in the blood-plasma in any of the cases.

Clotting time. Clotting of the blood did not occur at all in any of the cases.

Bleeding time. The figures given for the bleeding time show a wide variation. It was increased in four of the six cases in which the time is given. The cases of Rabe and Salomon (1920) and Opitz and Frei (1921) showed great prolongation, while Macfarlane's (1938) case had a bleeding time of 30 min. on one occasion and only 5½ min. on another. It was normal in our case and in that of Glanzmann, Steiner, and Keller (1940).

Blood platelets. Intermittent thrombocytopenia was observed in two of the seven cases. The patient of Glanzmann, Steiner, and Keller showed a minimum count of 35,000 and a maximum count of 275,000 per c.mm., while Macfarlane's case gave figures of 50,000 and 425,000 per c.mm. respectively. The platelet count was always within normal limits in the other five cases, including our own.

Capillary resistance. Rabe and Salomon (1920) suggested the likelihood of some unknown change in the vessels in this disease, but Macfarlane (1938) was the first to demonstrate diminished capillary resistance. Capillary resistance tests were not mentioned in most of the cases. The positive pressure method (Hess) demonstrated diminished capillary resistance in Macfarlane's case, but no abnormality was demonstrated by this method in our case. According to the negative pressure method of Scarborough (1941), which assesses capillary resistance in terms of the least negative pressure (in mm. of mercury) required to rupture capillaries in each of three standard areas of skin, the capillary resistance in our patient has always been found to be unduly low. The values found in our case are as low as any that we have observed. It is an important fact that although the negative pressure test consistently gave very low values for the capillary resistance, the positive pressure (tourniquet) test was negative. Bell, Lazarus, Munro, and Scarborough (1942) found a low order of correlation between the results of positive and negative pressure tests in 142 medical students. The negative pressure method had not been introduced when Macfarlane's (1938) case of afibrinogenaemia was published.

Blood sedimentation rate. A low blood sedimentation rate was demonstrated in both of the cases in which this test was done. In both Macfarlane's case and our own the rate was 1 mm. in one hour. Moreover, in our case sedimentation occurred at a constant rate (Table I); this aspect of the blood sedimentation rate was not investigated by Macfarlane.

Period of survival. The expectation of life is short. Four of the seven cases died in childhood, and none of the remaining three had passed beyond this period of life at the time of publication. There appears to be a great danger of fatal umbilical haemorrhage in the early days of life. This occurred in a sister of the boy whose case is recorded in the present paper and also in a sister of the boy whose case was reported by Macfarlane. The fibrinogen content of the blood was not estimated in these two infants

TABLE I

Results of the Principal Investigations Pertaining to the Haemorrhagic Diathesis of the Case Reported

Investigation	Plasma-fibrinogen	Clotting time	Bleeding time in minutes	Blood platelets per c.mm.	Haemoglobin %	Prothrombin estimation		Capillary resistance test		Serum-calcium mg. %	Blood sedimentation rate	Liver function tests	
Method used	Recalcification Micro-kjeldahl	Lee and White	Duke	Direct method	Haldane	Quick	Innes and Davidson	Positive pressure (Hess)	Negative pressure (Scarborough)		Westergren	Laevulose tolerance	Hippuric acid excretion test
27.5.1941	Nil No clot in 24 hr.	No clot in 24 hr.	2½	380,000	55	—	No coagulation	—	—	10·6	2 mm. in 1 hr.	1 hr., 7·5 mg. % 2 hr., 5 mg. % (normal figures)	—
1.6.1943	Nil (*a*) No clot in 24 hr. (*b*) No clot after adding viper venom (*c*) No precipitate with ½ saturated solution NaCl, but slight turbidity after 5 hr.	No clot in 48 hr.	2½	310,000	96	No coagulation	—	—	100 : 150 : 175 (resistance much reduced)	—	—	—	—
26.10.1943	Nil No clot in 72 hr.	No clot in 72 hr. (Macfarlane)	3	420,000	40	—	—	—	—	—	—	—	1·82 gm. % (subnormal)
18.4.1944	—	Fluid after 13 days in test tube	2	305,000	—	—	—	—	—	—	—	—	—
24.5.1944	Nil No clot in 24 hr.	—	2	398,000	—	—	—	Normal	100 : 100 : 100 (resistance much reduced)	—	—	—	3·17 gm. %
29.8.1944	—	No clot in 72 hr.	5	245,000	92	—	—	Normal	150 : 150 : 200 (resistance much reduced)	—	1 mm. in 1 hr. 4 mm. in 4 hr. 8 mm. in 8 hr.	—	—

because the possibility of a deficiency of fibrinogen was not suspected, but such a deficiency is likely to have been the cause of the haemorrhage. It seems probable, therefore, that a considerable proportion of the patients suffering from this disease die from umbilical haemorrhage in the early days of life without a diagnosis ever having been made.

Treatment. Haemorrhage should always be treated by rest in bed, and sedatives should be given to allay any nervousness. Trivial haemorrhages often subside with these measures, but more severe and persistent haemorrhage can be controlled only by intravenous transfusion with whole blood or blood-plasma. Care must be taken not to use processed plasma, for the fibrinogen is almost entirely removed during the processing of plasma in many blood banks.

Congenital Hypofibrinogenaemia

In addition to the seven recorded cases of congenital afibrinogenaemia, which have been analyzed in the present paper, four cases of congenital hypofibrinogenaemia have also been recorded. These four cases were reported by Risak (1934, 1935) and all were adults who were unrelated to one another. All had been 'bleeders' for most of their lives and there was a family history of a haemorrhagic diathesis in three of them. In each instance the blood-plasma contained only about one twentieth of the normal amount of fibrinogen. The principal clinical features of these cases are shown in Table III. It is remarkable that no further cases have been recorded since the publication 10 years ago of Risak's cases. The case recently reported by Allibone and Baar (1943) as an example of congenital hypofibrinogenaemia cannot with certainty be regarded as such; their patient had severe and extensive disease of the liver which may have accounted for the low plasma-fibrinogen.

A Comparison of Congenital Afibrinogenaemia and Congenital Hypofibrinogenaemia

Comparison of Tables II and III will show the principal distinctions between these two conditions, which are as follows:

Age at onset of haemorrhagic tendency. None of the records of the cases of congenital hypofibrinogenaemia states the age at which haemorrhagic manifestations first appeared; it was said to have been 'early life' in two cases and puberty in a third. In all the cases of congenital afibrinogenaemia it was present from birth or shortly afterwards. It seems likely, therefore, that the haemorrhagic state is not usually revealed as early when there is a small amount of fibrinogen as when there is none, but in the absence of accurate records this is largely a matter of conjecture.

Severity of haemorrhage. Both the frequency and the severity of the haemorrhage are considerably less in congenital hypofibrinogenaemia than when there is a total absence of fibrinogen.

TABLE II

The Principal Clinical Features of the Seven Reported Cases of Congenital Afibrinogenaemia

Authors	Sex	Age	Family history of haemorrhagic diathesis	Consanguinity of parents	Age at onset of bleeding tendency	Plasma-fibrinogen	Clotting time	Bleeding time	Blood-platelets per c.mm.	Capillary resistance test	Blood sedimentation rate	Period of survival	Cause of death
Rabe and Salomon (1920)	M	9 yr.	None known	1st cousins	14 days	Nil	No clot in 6 days	28 min. (Duke)	300,000	No record	No record	13 yr.	Haemorrhage
Opitz and Frei (1921)	F	8 mon.	None known	None known	'From birth'	Nil	No clot in 2 hr.	40+min. (Duke)	1,030,000	No record	No record	8 mon.	Haemorrhage
Macfarlane (1938)	M	9 yr.	Yes (sister)	1st cousins	'From birth'	Nil	No clot in 3 weeks	5½ to 30+min. (Duke)	50,000 to 425,000	Hess, pos.	1 mm. in 1 hr. 2 mm. in 4 hr.	Alive	—
*Schönholzer (1939)	M	12 yr.	—	—	'From birth'	Nil	No clotting	Increased	334,000	—	—	4 yr.	Cerebral haemorrhage
*Schönholzer (1939) (Fritzsche)	F	2½ yr.	—	—	'From birth'	Nil	No clotting	No record	180,000	—	—	2½ yr.	Haemorrhage
Glanzmann, Steiner, and Keller (1940)	M	3 yr.	None known	None known	'From birth'	Nil	No clot in 24 hr.	5 min.	35,000 to 275,000	No record	No record	Alive	—
Authors' case (1945)	M	11 yr.	Yes (sister)	1st cousins	3 days	Nil	No clot in 13 days	2 to 5 min. (Duke)	245,000 to 420,000 (Direct)	Hess, neg. Scarborough, pos.	1 mm. in 1 hr. 4 mm. in 4 hr. 8 mm. in 8 hr. (Westergren)	Alive	—

* The authors were unable to consult the original published records of these two cases, which were not available owing to war conditions. This explains the absence of the family history and other data.

TABLE III

The Principal Clinical Features of the Four Reported Cases of Congenital Hypofibrinogenaemia

Author	Sex	Age	Family history of haemorrhagic diathesis	Consanguinity of parents	Age at onset of bleeding tendency	Plasma-fibrinogen gm. %	Clotting time (Schultze)	Bleeding time (Duke)	Blood platelets per c.mm.	Capillary resistance test (Rumpel-Leede)	Blood sedimentation rate	Period of survival
Risak (1934)	F	41 yr.	Yes (son, fibrinogen 0·02 gm. %)	None known	'Early life'	0·018	5 min.	1½ min.	144,000	Negative	12 mm. in 1 hr.	Alive
,, ,,	F	22 yr.	Yes (a brother's clotting time was 13+ min.)	,, ,,	No record	0·019	4 min.	5 min.	99,000	Negative	15 mm. in 1 hr.	Alive
,, (1935)	F	71 yr.	Yes (son)	,, ,,	'Early life'	0·018	*4 to 12 min.	4½ min.	120,000	Positive	8 to 13 mm. in 1 hr.	Alive
,, ,,	F	37 yr.	None known	,, ,,	? Puberty	0·018	5 min.	3 min.	400,000	No record	No record	Alive

* The author stated that coagulation began at 4 min. and was complete in 12 min. This may represent a slight increase of the coagulation time.

Consanguinity. This feature did not occur in any of the four reported cases of congenital hypofibrinogenaemia, whereas it occurred in three of the seven cases of congenital afibrinogenaemia.

Fibrinogen. Only about a twentieth part of the normal amount of fibrinogen was found in each of the four cases of congenital hypofibrinogenaemia. Three of these had 0·018 gm. per cent. (normal range 0·2 to 0·4 gm. per cent.). As the name implies, none was found in any of the cases of congenital afibrinogenaemia.

Clotting time. This was normal in all four cases of congenital hypofibrinogenaemia, but clotting did not occur after a prolonged period in any of the cases of congenital afibrinogenaemia. The presence of a normal clotting time in congenital hypofibrinogenaemia, in which only about 5 per cent. of the normal amount of fibrinogen is found, appears to eliminate fibrinogen deficiency as a possible cause of an increased coagulation time in diseases showing less severe degrees of hypofibrinogenaemia.

Bleeding time. This also was normal in all four cases of congenital hypofibrinogenaemia. It was increased in four of the six cases of afibrinogenaemia in which it was recorded, but it was normal in the remaining two cases.

Blood platelets. The platelet count was low in three of the four cases of congenital hypofibrinogenaemia, but in only two of the seven cases of congenital afibrinogenaemia.

Capillary resistance. The positive pressure test (Rumpel-Leede) demonstrated diminished capillary resistance in only one of the three cases of congenital hypofibrinogenaemia in which it was done. A similar lack of uniformity was found in congenital afibrinogenaemia, for although it was done in only two cases it was positive in one and negative in the other. No comparison can be made with the negative pressure test, which was done only in our case of congenital afibrinogenaemia.

Blood sedimentation rate. This was reported by Risak (1934) to have been normal in each of the three cases of congenital hypofibrinogenaemia in which it was estimated (the figures were 8 to 13, 12, and 15 mm. in one hour respectively), but it was low in the two cases of congenital afibrinogenaemia in which the test was done (the figure was 1 mm. in one hour in each instance). Since the fibrinogen level in the blood-plasma is believed to have more influence on the blood sedimentation rate than any other factor, such a pronounced difference in the blood sedimentation rate in the two conditions is surprising in view of the fact that the blood-plasma of the patients with congenital hypofibrinogenaemia contained only about one-twentieth of the normal amount of fibrinogen.

Period of survival. The expectation of life appears to be good in congenital hypofibrinogenaemia, whereas it is poor in congenital afibrinogenaemia. All of the four reported cases of the former disease were in adults—two were middle-aged and one 71 years—and all were still alive, but all seven of the patients with a total lack of fibrinogen were children, of whom four had already died.

Comment

The term fibrinogenopenia and the abbreviated term fibrinopenia are commonly applied to all cases with an abnormally low fibrinogen or an absence of fibrinogen in the blood-plasma. The normal range of plasma-fibrinogen in healthy persons is between 0·2 and 0·4 gm. per cent., although the latter figure is frequently exceeded. It seldom falls much below 0·2 gm. per cent. An increased level of fibrinogen occurs in a variety of diseases, particularly the infections. An abnormally low plasma-fibrinogen is much less common and the causes of it are, therefore, less well known. It appears from the literature that the less severe degrees of fibrinogenopenia are acquired, whereas the severe degrees with little or no fibrinogen in the plasma may be either congenital or acquired. Congenital fibrinogenopenia is probably caused by a hereditary defect of fibrinogen formation, whereas the acquired type is caused by some toxic or neoplastic interference with fibrinogen formation.

Schönholzer (1939) has suggested that congenital afibrinogenaemia and congenital hypofibrinogenaemia may be variants of the same hereditary disease, and that the parents of patients with the former disease are homozygous, while those of patients with the latter are heterozygous. We believe that the relationship, if any, between the two diseases cannot be clarified until a much larger number of cases has been investigated.

Numerous examples of acquired fibrinogenopenia have been published and several have shown a complete absence of fibrinogen. Opitz and Silberberg (1924) found no fibrinogen in a three-year-old girl with generalized tuberculosis in whom the liver was mostly replaced by caseous masses, and Jürgens and Trautwein (1930) found less than 0·1 gm. per cent. with no clotting in 48 hours, in a man of 52 years with widespread prostatic metastases in the bone-marrow. Allibone and Baar (1943) reported temporary afibrinogenaemia in an infant with congenital obliteration of the bile ducts, and Knauer (1927) recorded the case of a girl of six years suffering from *purpura fulminans* whose blood showed no clotting after three days and a fibrinogen content of 0·015 gm. per cent. Glanzmann, Steiner, and Keller (1940) reported temporary afibrinogenaemia in a case of transitory haemorrhagic diathesis associated with haemolytic anaemia in an eight-months-old female infant. These cases of severe acquired fibrinogenopenia throw some light on the site of fibrinogen formation, and suggest that both the liver and bone-marrow are concerned with this function. Confirmatory experimental evidence of such an origin has also been adduced (Müller, 1905; Mann and Magath, 1922; Jürgens and Gebhardt, 1934; Keilhack, quoted by Jürgens, 1938). The whole reticulo-endothelial system may be concerned with fibrinogen formation, but this is at present a matter of speculation. The association of thrombocytopenia with fibrinogenopenia which has been observed in some cases might be thought to support the view that a disturbance of marrow function exists in congenital fibrinogenopenia.

Several workers have speculated on the fibrinogen level below which a haemorrhagic state appears, and a few investigators have attempted to define the threshold experimentally. Jürgens and Trautwein (1930) postulated a threshold lying between 0·12 and 0·15 gm. per cent., and Risak (1935) believed it to be about 0·1 gm. per cent. Macfarlane (1938) and Allibone and Baar (1943) have shown experimentally that the critical level is probably about 0·06 gm. per cent., but the latter workers, like Klinke (1938), showed that there is mutual compensation within certain limits among some of the factors concerned with coagulation of the blood. This fact seems to account for the very low fibrinogen threshold of about 0·06 gm. per cent.

A puzzling feature of the case of congenital afibrinogenaemia reported in the present paper is the spontaneous arrest of bleeding, within a comparatively short time after the extraction of two teeth (see p. 102), while at other times the cutting or shedding of teeth caused persistent oozing of blood which lasted for several days. We are doubtful as to the correct interpretation to be placed upon these facts. Such behaviour emphasizes the necessity for care in the interpretation of observations in patients suffering from this disease and in the assessment of the effect of treatment.

It has always been assumed that the bleeding tendency in cases of afibrinogenaemia is due to the absence of fibrinogen, but it seems that a low degree of capillary resistance is also a feature of the disease, which may in part account for some of the haemorrhagic manifestations. There is not enough evidence to show whether intermittent thrombocytopenia contributes to the haemorrhagic tendency (Allibone and Baar, 1943), but the presence of a normal platelet count at the time of haemorrhage in most of the cases shows that it is unimportant.

Summary

1. A case of congenital afibrinogenaemia, which is a rare cause of the haemorrhagic diathesis, is reported in a boy aged 11 years.

2. Six other cases which have been recorded in the literature are reviewed.

3. The principal clinical features of congenital afibrinogenaemia are its hereditary character, a high incidence of consanguinity in the parents, the susceptibility of both sexes, a total absence of fibrinogen in the blood, complete incoagulability of the blood, a bleeding time which is usually prolonged, a great reduction of capillary resistance, a low blood sedimentation rate, and intermittent thrombocytopenia.

4. Treatment of the severe haemorrhage is by intravenous transfusion with whole blood or non-processed plasma.

5. Absence of fibrinogen is regarded as the principal cause of the haemorrhagic diathesis in congenital afibrinogenaemia, but diminished capillary resistance may be a contributory factor.

6. Four cases of congenital hypofibrinogenaemia which have been recorded in the literature are also reviewed.

7. The principal distinctions between congenital afibrinogenaemia and congenital hypofibrinogenaemia are discussed. The clotting time shows the greatest divergence; no clotting occurs in afibrinogenaemia, whereas it is normal in hypofibrinogenaemia.

8. The aetiology of both the congenital and acquired forms of afibrinogenaemia and of hypofibrinogenaemia is discussed.

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616.61–003.84

NEPHROCALCINOSIS ASSOCIATED WITH HYPERCHLORAEMIA AND LOW PLASMA-BICARBONATE[1]

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With Plate 6

In 1936, Butler, Wilson, and Farber drew attention to a clinical syndrome characterized by persistent dehydration in the absence of excessive diarrhoea and vomiting and the presence of adequate food, salt, and water intake, a persistent hyperpnoea associated with sustained elevation of the serum-chloride concentration, reduction of the serum-bicarbonate content, and lastly deposits of calcium salts within and adjacent to certain renal tubules. This syndrome occurred in four infants of ages varying from a few weeks to six months old. As an appendage to their paper they described one further case of a 10-year-old boy with advanced rickets, bilateral renal stones, and similar biochemical findings, but without any hyperpnoea.

In 1940, Albright, Consolazio, Coombs, Sulkowitch, and Talbott reported the case of a 13-year-old girl with persistent rickets and dwarfism. This patient also had massive calcium deposits in the pyramids of the kidneys, hyperchloraemia, and a low serum-bicarbonate level. After extensive metabolic studies, it was concluded that the syndrome was a renal tubular disorder with inability to secrete ammonia or to excrete an acid urine, shortage of base with which to excrete mineral acids, specially the chloride radicles, increased calcium loss in the urine acting as a base, secondary hyperparathyroidism to meet the tendency of low serum-calcium, hypophosphataemia, and 'low phosphorus rickets'.

Boyd and Stearns (1941) under the title 'Concomitance of chronic acidosis with late rickets', described an 11-year-old girl with essentially similar metabolic findings. This patient died unexpectedly, and the autopsy showed only slight calcium deposits in the pyramids whilst the tubules were essentially normal, though the convoluted tubules were considerably dilated. The findings in this case suggested that nephrocalcinosis was not an essential part of the syndrome. Boyd and Stearns postulated that the cause was a 'perversion of her whole electrolytic system rather than a primary tubular dysfunction'.

Rule and Grollman (1944) reported a further case in a girl. She had suffered from rickets and spontaneous fractures since the age of 15 months,

[1] Received January 28, 1945.

and when first seen at the age of 15 years was unable to walk. Investigations showed multiple renal calculi, low plasma-phosphorus, hyperchloraemia, low serum-bicarbonate, and relatively fixed specific gravity of the urine.

We have had under observation a 29-year-old woman with similar metabolic findings and kidney lesions, but without skeletal changes. Although

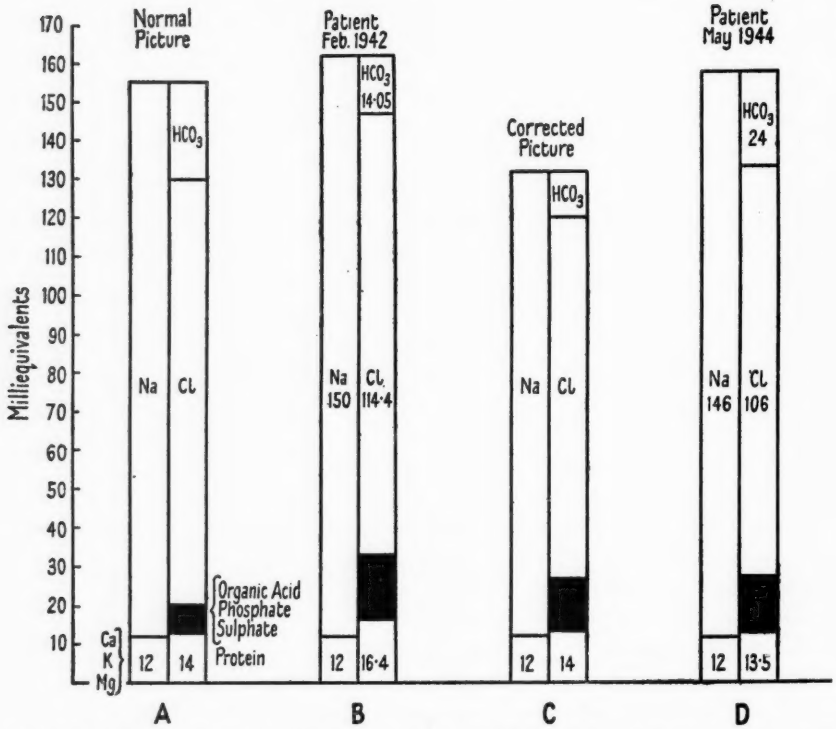

FIG. 1 depicts the electrolyte pattern of the patient in 1942 and in 1944, comparing it with the normal. The amount of calcium, potassium, and magnesium have been assumed to remain constant at 12 m. eq. C is the suggested correct pattern in 1942 when allowances have been made for the increased serum-proteins in maintaining osmotic pressure in the plasma. In both 1942 and 1944 there is an increase in the organic acids, phosphate, and sulphate components. The lack of any marked alteration in this fraction suggests that there has been no change in the kidney function over the past two and half years.

she is considerably older than the other reported cases and has no bone lesion, we consider that the underlying disorder is probably the same.

Case Report

The patient, aged 29 years, was first seen by one of us (G.H.B.) in 1940 on account of ureteric colic. At that time she felt well and was carrying out the duties of a staff nurse. She had had no serious illness and her childhood had been uneventful. On questioning, she stated that she had suffered with polyuria and thirst since the age of 10 years so that she considered these

symptoms to be part of her normal make-up. She had had no symptoms in the past suggestive of pyelonephritis or cystitis, and had never taken excessive amounts of vitamin D. For some years she had had soreness of the corners of the mouth during the winter months and, in addition, had had a sore tongue over the previous two years.

Her mother, two brothers, and sister were healthy, and did not suffer from thirst or polyuria. Her father, however, is stated to have died of renal stones at the age of 45 years, but no further details are available.

Since first being seen in 1940, the patient has had a few attacks of ureteric colic and has passed small calculi. She has also had occasional attacks of upper respiratory infection, but otherwise has been carrying out her nursing duties. She drinks a large amount of water daily, usually waking during the night for a drink. Menstruation started at 12 years, and is regular every 27 days, lasting for four days.

In appearance, she was moderately well built, height 5 ft. 7 in. and weight 7 st. 10 lb. Her skin was of good texture with no pigmentation, hyperkeratosis, or other abnormality. The teeth were in good condition. No abnormality was detected in the heart, lungs, or central nervous system. Her blood pressure was 110/70.

Preliminary investigations. An X-ray (Plate 6, Fig. 2) showed multiple stones throughout both kidneys. An intravenous pyelogram showed that the stones were situated in the pyramids and that there was little to be seen in the kidney substance itself. The kidney pelves had not undergone any marked dilatation (Plate 6, Fig. 3). X-rays of the femur, humerus, pelvis, tibiae, and skull showed no evidence of decalcification. The appearance of the sella turcica was normal.

Numerous urine examinations have shown amounts of albumen varying from the merest trace to moderate quantities. Microscopical examination has shown only pus and red blood cells. Several bacteriological examinations have been negative, and inoculation of guinea pigs has been negative for the tubercle bacillus. The urine contained no cystine, sugar, or ketone bodies. Estimations of the pH on six occasions showed it to vary between 6·7 and 7·1. A ketogenic diet and ammonium chloride (45 gr. daily) depressed the pH only to 6·3.

An initial urea clearance test in 1940 showed 45 per cent. of normal function, whilst a urea concentration test gave the following readings:

1st specimen:	295 c.c.	Urea concentration	1·4	per cent.
2nd „	59 „	„	1·3	„ „
3rd „	226 „	„	0·7	„ „

Twelve months later a second test showed:

1st specimen:	950 c.c.	Urea concentration	1·7	per cent.
2nd „	64 „	„	1·6	„ „
3rd „	230 „	„	1·6	„ „

Her blood count showed red cells 4,500,000 per c.mm., white cells 11,000 per c.mm., and haemoglobin 58 per cent. The count rapidly returned to normal levels with iron therapy. The blood-urea varied between 35 and 45 mg. per 100 c.c. Serum-calcium was 11·0 and 12 months later 10·0 mg. per 100 c.c. with the serum-phosphorus 1·8 and 3·2 mg. per 100 c.c. and the serum-phosphatase 8 and 13 units respectively. The serum-chloride was raised, 660 mg. per 100 c.c. (113 m.eq.), while the plasma carbon dioxide combining power was low, 32 vol. per cent. (14·3 m.eq.). These preliminary investigations suggested that this might be a further case of the syndrome so fully investigated by

Albright, Consolazio, Coombs, Sulkowitch, and Talbott (1940). More detailed observations were therefore made.

Calcium balance. On a diet containing 0·457 gm. of calcium and 0·757 gm. of phosphorus per diem for six days, the following results were obtained during the last three days of the test.

	Urinary calcium	Faecal calcium	Urinary phosphorus
4th day	294 mg.	533 mg.	691 mg.
5th „	277 „	per diem.	570 „
6th „	262 „		624 „

There was therefore a negative balance of 387 mg. of calcium daily.

Cholesterol excretion in a 24-hours specimen of urine on a normal hospital diet was within normal limits, 10 mg.

Respiration. Several examinations of the ventilation rate and alveolar air were made. After 10 hours sleep, the ventilation rate was 4·17 l. per minute, and when not under basal conditions 4·87 l., with an alveolar carbon dioxide of 25·8 mm. and alveolar oxygen of 107 mm. of mercury. The respiration rate was between 15 and 16 per minute.

Urinary excretion. In Table I a detailed analysis of the urine over 24 hours on a restricted fluid intake is given. Both the pH and the specific gravity are relatively fixed. Ammonia excretion is low. These examinations were repeated while the patient was taking 20 gm. daily of a sodium citrate-citric acid mixture (Albright, Consolazio, Coombs, Sulkowitch, and Talbott, 1940),[2] but no appreciable change was detected. When she took 40 gm. daily and fluids there was again no essential change (Table II).

TABLE I

No.	Time	Volume c.c.	pH	Sp. gr.	Acid c.c. 0·1 N	Ammonia c.c. as 0·1 N acid	$NaHCO_3$ as 0·1 N alkali	Free CO_2	Chlorides as NaCl mg. %	P. mg. %
	a.m.									
1	6.30	215	6·74	1004	13·8	26·0	6·8	26	380	47·6
2	8.30	175	6·73	1007	9·6	16·4	5·6	26	255	44·4
3	10.30	100	6·76	1005	5·5	10·0	3·2	22·8	310	40·0
	p.m.									
4	12.30	120	6·62	1006	9·2	13·1	3·0	29·2	235	45·2
5	2.30	135	6·66	1007	9·1	13·7	3·4	29·2	260	43·3
6	4.30	190	6·88	1006	9·4	16·8	3·6	29·2	310	25·8
7	6.30	212	6·86	1006	7·8	19·1	6·3	29·2	330	22·7
8	8.30	165	6·76	1004	5·2	17·5	3·0	16·2	250	30·2
9	10.30	245	6·80	1007	9·3	23·6	7·6	22·7	330	24·3
10	Night	285	6·87	1007	9·3	37·5	10·0	22·7	300	20·5
		1842			88·2	193·7	52·5			

1.5.42. Acid + ammonia − bicarbonate = 230 c.c. 0·1 N acid.
Total phosphorus (as phosphorus) 667 mg.
Total sodium chloride 6·7 gm.

Blood analyses. In Table III the various blood analyses are given. Over the first 20 months of observation, during which the anaemia was corrected and the citric acid mixture taken intermittently, no change was noted.

[2] Citric acid 140 gm.
Sodium citrate 98 gm.
Water to 1000 c.c.

After two weeks steady administration of 40 gm. daily of the mixture, the acid-base balance approached normal values and the serum-proteins began to return to normal levels.

TABLE II

No.	Time	Volume c.c.	pH	Total chlorides	Total phosphorus	Sp. gr.	Ammonia mg.
1	8.50	90	6·73	170	37·8	1005	3
2	10.35	270	6·77	430	97·5	1004	8·9
3	1.20	270	6·86	570	130	1005	10·5
4	4.00	300	6·84	696	93	1005	10·5
5	5.30	400	7·14	840	96	1005	13·2
6	7.30	350	7·16	785	91	1003	12·2
7	9.25	350	7·08	925	115	1007	10·7
8	11.30	300	7·08	945	84	1005	10·5
	midnight						
9	3.30	280	7·08	661	98	1004	11·5
10	7.30	430	7·18	945	258	1005	15

May 1944. 24-hour urine — Vol. 3040 c.c.
Total phosphorus (as phosphorus) 6·1 gm.
Total sodium chloride 6·9 gm.
Total ammonia 106 c.c. N/10 acid.

TABLE III

	1940–1	16.2.42	23.2.42	30.4.42	1.3.43	4.5.43	24.11.43	1.12.43	16.5.44
	No treatment		Citric acid mixture 20 gm. daily	Citric acid mixture 40 gm. daily, intermittently		Attack of renal colic	Citric acid mixture 40 gm. daily, regularly		
Blood urea	38–46	43	45	44	51	43	41	49	58
Non-protein nitrogen	—	32	—	—	—	30	—	—	—
Serum-cholesterol	—	137	—	—	182	—	—	—	—
„ NaCl	660	656	670	680	660	658	624	624	618
	112·9 m. eq.	112·1	114·4	116·2	112·9	112·6	106·5	106·5	106
„ calcium	11·0–10	11·9	—	—	9·0	10·2	10·2	—	10·8
„ phosphorus	1·8–3·2	2·8	—	2·1	2·8	2·5	3·0	—	3·9
„ phosphatase	8–13	10·8	—	—	10·4	—	—	—	—
„ potassium	—	—	20	—	—	—	—	—	—
„ sodium	—	—	345	—	—	315	335	336	335
„ albumen	—	—	5·7	—	5·75	6·0	4·6	—	4·3
	—	—	16·43 m. eq.	—	—	—	13·76 m. eq.	—	13·1
„ globulin	—	—	3·8	—	3·75	3·0	3·7	—	3·5
Plasma-creatinine	—	—	1·2	—	—	—	—	—	—
„ CO_2 (vol.)	32·0	32·0	31·5	36	35	35	50	57·5	53·5
„ CO_2 (m. eq.)	14·3	14·3	14·05	15·6	15·6	15·6	22·3	25·7	23·95
„ pH	7·42	7·24	7·3	7·24	7·2	7·32	7·36	7·34	7·44

Urinary calculi. Chemical analysis of the calculi showed the presence of calcium, phosphate, and carbonate with amounts of cholesterol up to two per cent. in some specimens. There were no halogens present. The X-ray diffraction pattern showed that they were essentially similar or identical in composition with 'dahlite', that is, they could not be distinguished from bone. They were freely soluble in a solution of magnesium oxide and citric acid (solution G of Suby and Albright, 1943), a point which may be of value in other cases when therapy is under consideration.

Present status, 1944. For the past two years the patient has been working full time as the staff nurse in a busy surgical ward. She has had one attack of severe ureteric colic (May 1943), after which she passed a number of small stones. For the past six months she has been taking the citric acid mixture regularly. Her weight has now increased to 8 st. 1 lb. Her present metabolic state is set out in the last column of Table III. Several X-rays over the past four years show very little change in the size of the stones. She states that her general health is better now than it ever has been before in spite of her working harder.

Discussion

The gross disturbance of electrolyte balance in this patient can well be shown by graphic representation (Fig. 1). The striking feature is the increase of chlorides at the expense of the serum-bicarbonate. There are three theoretical explanations for this increase, firstly an alteration of intestinal habit leading to increased absorption of chloride or loss of base without accompanying chloride, secondly hyperpnoea, and lastly a relative loss of the ability to excrete chlorides by the kidneys. The first reason can be ruled out since there has never been any suggestion of intestinal upset in this case. According to Peters and Van Slyke (1931), hyperpnoea may lead in some cases to a fall in serum-bicarbonate and rise in serum-chloride. In the infants reported by Butler, Wilson, and Farber (1936) hyperpnoea was present, but in our patient there was no evidence of this. It seems, therefore, that the kidney itself must provide the explanation for the maintenance of this metabolic state. Albright, Consolazio, Coombs, Sulkowitch, and Talbott (1940) indicate that the inulin clearance is low, as also are the creatinine and urea clearances. Their argument that the low clearances of the last two substances are due to the tubular damage appears unwarranted, inasmuch as the fall from normal values is proportional to the fall of inulin clearance. This indicates that a certain number of nephrons are completely out of action, presumably blocked by calcium. Such a condition would explain the polyuria, the fixed specific gravity, and the inability to secrete ammonia. There are, however, two good reasons for rejecting this hypothesis. Experimentally, one has to destroy at least two-thirds of the kidney substance to produce these urine changes. From the urea clearance figures of the two reported cases (Albright, Consolazio, Coombs, Sulkowitch, and Talbott, 1940; Rule and Grollman, 1944) and of our patient, this certainly is not true. Furthermore, if a large amount of kidney destruction were present, a condition of hypochloraemia and not hyperchloraemia would be present (Peters and Van Slyke, 1931).

Albright and his colleagues suggested that the kidney in this condition is unable to excrete acid. Although, in our case, titrable acid appears to be low, we have no adequate standards of acid excretion, and as Blatherwick (1914) has pointed out, measuring intake does not help. There is, too, no great increase in the acid fraction of the serum. The ratio of decinormal ammonia to decinormal acid in the urine is well above the lower limits of

normal. If there is a deficit in acid secretion, we would postulate that it is partly due to an attempt to conserve base. Boyd and Stearns (1941) pointed out the inability of the body to conserve water and excrete ammonia in sufficient quantity to conserve base. They considered that this might be attributable to a perversion of the whole pattern of electrolyte and water control rather than to a primary derangement of the renal tubules. This possibility cannot be dismissed. Hyperchloraemia has been reported in diabetes insipidus and it is conceivable that a mild state of diabetes insipidus over a prolonged period of time might eventually lead to calcium deposition and secondary tubular damage, and so to the extreme upset of metabolism present in our patient. Adrenal hormones may also give rise to alterations in chloride and water metabolism (Thorne and Engel, 1938; Ragan, Ferrebee, Phyte, Atchley, and Loeb, 1940), but there was no evidence that such hormones were playing any part in our patient's illness.

In the absence of evidence of reticulo-endothelial involvement, we have regarded the raised serum-protein as an attempt to preserve the osmotic pressure of the serum, as is seen in states of dehydration. If we assume that this is the position and portray the electrolyte picture with the proteins adjusted to a normal level of 7 gm. per cent., it will be seen that there is actually a deficit of base in spite of a normal or slightly elevated serum-sodium. Such a finding would not be unexpected from our interpretation of the urinary excretion of electrolytes. In Albright, Consolazio, Coombs, Sulkowitch, and Talbott's case the total proteins were 6·5 gm. per cent., but were not recorded in the other three reported cases. The suggestion that the raised protein is a manifestation of dehydration and lack of base is strengthened by the return to normal values with the provision of extra sodium.

In the patient of Butler, Wilson, and Farber, analysis of the stone showed it to be a calcium-phosphate-carbonate compound of the composition of bone. It is probable that this stone was similar to that found in our patient. Our analysis revealed that there was only a minimum of organic matrix (as shown by the cholesterol content). Compounds of this type are formed in neutral or slightly alkaline solutions (Logan, 1940). The exact mode of formation must remain undecided at present. Similarly, the site of deposition is not known with certainty. Butler, Wilson, and Farber reported that when nephrolithotomy was attempted in their older patient the calcification was so diffusely and intimately associated with the renal parenchyma that separation was impossible. At the autopsy on Boyd and Stearns's case the convoluted tubules were considerably dilated, though the epithelium was well preserved and showed only mild vacuolation. There were a few small areas of calcium deposition in the pyramids. In the infants reported upon by Butler, Wilson, and Farber the earliest lesion appeared to be calcium deposition within the walls of the collecting tubules, between the basement membrane and the epithelial cells, and within the connective tissue surrounding the tubules. Deposits of calcium were rarely found in the proximal collecting

tubules. In these cases, which may not have been essentially the same syndrome as the case we are considering, rings of an organic matrix could be seen in the calcium deposits. It is possible, as we have stated, that the calcium deposition was not an essential part of the syndrome and that the few pathological observations available support the metabolic observations that the tubules are at fault.

Albright, Consolazio, Coombs, Sulkowitch, and Talbott secured good symptomatic results in their case with a sodium citrate-citric acid mixture. Under carefully controlled metabolic conditions, they found that a high calcium and phosphorus, low chloride diet combined with 40,000 units of vitamin D2 daily and 60 c.c. (12 gm.) of citrate mixture produced a rise of serum-bicarbonate from 14·2 to 20·1 m.eq., though the chloride did not change much, from 114·1 to 112·3 m.eq. It should also be noted that when the patient was first seen, before treatment, the serum-bicarbonate was 19·3 m.eq. The patient was discharged on this therapy though with a much reduced dosage of vitamin D. During the next nine months she grew three inches in five months, whereas in the previous eight months she had grown only one inch. She had also become maturely built with developed breasts and had had her first menstrual period. X-rays showed that new bone had been laid down, contrasting sharply with that laid down prior to treatment, and the kidney lesions appeared to have decreased. The serum-phosphorus had risen to normal levels from 2·1 to 4·1 mg. per 100 c.c. The serum-chloride was only slightly elevated, 107 m.eq., the carbon dioxide combining power was still 19·6 m.eq., and the urinary specific gravity and pH were still relatively fixed. It is difficult to evaluate the coincidental factors that may have played some part in this case. The increase in the serum-phosphorus, whether due to vitamin D or improved tubular resorption, undoubtedly led to the improvement in the skeletal condition. Similarly, whether the improvement of the chloride acidosis was brought about by increased base provision or by a functional improvement in the tubular physiology due to the onset of menstruation are possibilities to be considered. Rule and Grollmen (1944) used the same therapy as Albright and his colleagues in their case and reported a striking improvement in the skeletal condition, the patient being enabled to walk. The biochemical findings, however, did not show any great improvement, the carbon dioxide combining power rising from 26 vol. (11·6 m.eq.) to 36 vol. per 100 c.c. (16·1 m.eq.). As would be expected from the improvement in the skeletal condition, the calcium and phosphorus values rose from 9 and 2·7 to 11·5 and 6·0 mg. per 100 c.c. respectively.

In our patient the serum-phosphorus has tended to be low, but with therapy has returned to normal levels. A possible interpretation is the correction of acidosis, allowing the more adequate reabsorption of phosphate by the tubules. There appears to be no need to postulate a secondary hyperparathyroidism in any of the reported cases, as suggested by Albright, Consolazio, Coombs, Sulkowitch, and Talbott (1940) in their case. The calcium balance study in our case showed that the decalcification must take

place. The lack of any radiological evidence, however, must indicate an adequate replacement when on an unrestricted and self-selected diet. At first with therapy, only subjective improvement was obtained, but with increase in dosage a return to an approximately normal electrolyte picture was obtained. Nevertheless, though the blood changes had returned to normal, the urinary findings showed no real alteration. The specific gravity and pH were still constant. From the results of reported cases and particularly of our patient, it seems that the improvements are due almost entirely to the provision of extra base, and that the tubules, as Albright and his colleagues have suggested, are incapable of forming sufficient ammonia to allow the excretion of acid radicals without excessive loss of vital basic elements. With the provision of extra base also, the necessity for raised serum-proteins to maintain the osmotic pressure of the plasma disappears, with their consequent return to normal values.

Even if the main electrolyte changes and effects become clear, it is still not obvious whether the tubular dysfunction is primary or secondary to endocrine factors, metabolic errors, or local inflammatory lesions such as nephritis. The existence of polyuria for at least 20 years in our patient seems to rule out a nephritic lesion. Furthermore, cases of hyperchloraemic nephritis (Peters, Wakeman, and Lee, 1929) bear little resemblance to this syndrome. Albright and his colleagues have rightly compared the condition to the cases reported by Fanconi (1931, 1936) of children with resistant rickets, acidosis, and glycosuria. Similar cases reported subsequently have been reviewed by McCune, Mason, and Clarke (1943), and seem to substantiate Fanconi's suggestion that the kidney itself might be the aetiological factor. Hunter (1935) reported two cases with osteomalacia, low serum-phosphorus, and renal glycosuria, while we have had under observation a similar patient in whom we were able to show that the tubules were unable to reabsorb normal amounts of phosphorus. There is, too, the common renal glycosuria, a defect of tubular function. There seems then to be no reason against the supposition that one or many of the tubular functions may be defective. The death of our patient's father from renal stones, though details are lacking, raises the possibility of an inherited defect. Further work is necessary before it will be possible to assign to any circulating hormone or metabolic error a primary role in the production of these syndromes.

Summary

1. The case history and metabolic findings of a 29-year-old woman with polyuria, extensive bilateral renal stones, raised serum-chlorides, low plasma-bicarbonate, and relatively fixed specific gravity and pH of the urine are described.

2. With a sodium citrate-citric acid mixture the patient regained good health and her blood chemistry findings became approximately normal. Kidney function remained unchanged.

3. Four similar cases from the literature, but arising before puberty, are reviewed. It is concluded that they form one of the syndromes brought about by a defect in tubular function. The basis is an inability of the tubules to form sufficient ammonia to allow the excretion of acid radicals without the loss of vital basic elements. The defect may be compensated for by the provision of extra base.

4. It is considered unlikely that the tubular defect is inflammatory in origin, but there is insufficient evidence at present to assign a definite reason for the tubular dysfunction.

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APPENDIX

Methods of Estimation

Blood. The following methods have been used in analysis: Blood-urea, Twort and Archer; non-protein nitrogen, Folin and Wu; cholesterol, modification of Myer-Wardell method; calcium, Kramer and Tisdall; phosphorus, Kuttner and Cohen; phosphatase, Jenner and Kay; potassium, Peters and Van Slyke; sodium, Eisermann's modification of Kramer and Gittleman's method; albumen and globulin, colorimetric method of Wu and Ling; creatinine, Folin and Wu; plasma-carbon dioxide, Peters and Van Slyke; plasma pH, electrometric method; chlorides, modified Volhard method.

Urine. Bicarbonate was measured by Van Slyke manometer; pH by glass electrode; chlorides by Volhard-Harvey method; ammonia by the Van Slyke aeration method or the Conway units; cholesterol by the colorimetric method of Peters and Van Slyke.

ADDENDUM

In April 1945, after a short illness, the patient died. Death appears to have been precipitated by a severe reaction to sulphathiazole. Preliminary histopathological examination of the kidneys showed calcification in the pyramids and renal pelvis, but negligible amounts within the tubules and kidney tissues. The tubules themselves showed extensive vacuolation and an alteration in the type of epithelium. Occasional glomeruli were atrophied. There was no evidence of primary chronic vascular disease or glomerulonephritis. The findings, which will be reported in full later, appear to support the suggestion of tubular dysfunction set out above.

FIG. 2

FIG. 3

616.36–008.515 : 614.4

THE EPIDEMIOLOGY OF INFECTIVE HEPATITIS IN SOME UNITS OF THE BRITISH ARMY IN SICILY AND GREAT BRITAIN, 1943–4[1]

By A. M. McFARLAN

Epidemics of jaundice were apparently known to the Hippocratic physicians (Cockayne, 1912) and since the middle of the eighteenth century many epidemics have been reported from all over the world (Hirsch 1864; von Bormann, Bader, Deines, and Unholtz, 1943). In some of these outbreaks jaundice may have been a complication of some other infection or due to leptospiral infection, but many appear to have been due to the disease which is now known as infective hepatitis. There is some evidence of a long-term variation in prevalence, for Gibson (1913) found records of many epidemics in England in 1888–94 and again in 1910–13 with few in the intervening years. In the United States of America there were only a few recorded outbreaks in the Southern States between the epidemic during the civil war of 1851–6 and 1886. Between that year and 1920 there were at least 50 outbreaks, some of them in the Northern States. In 1920 there was a further increase which culminated in 1921–2 with 200 outbreaks in New York State (Blumer, 1923). Since that time the disease has apparently been less prevalent in the United States, but there have been epidemics in the Scandinavian countries, Germany, and Great Britain. Most of the British epidemics affected rural areas, but in 1942–3 cases were reported in Wolverhampton (Edwards, 1943) and an epidemic in Wembley (Ford, 1943).

The statistical epidemiology has not been fully worked out, although valuable figures are available for Sweden where the disease has been notifiable since 1931 (Selander, 1939). In England epidemics are most frequent among children of school age in rural districts. In some epidemics adults between 20 and 30 years have been chiefly affected (Gibson, 1913). No age is exempt, but the disease is rare in children under five years. Epidemics are most common in autumn and winter and are usually prolonged over several months. A few explosive outbreaks have been reported. Multiple cases in households are more frequent than they would be on a random distribution, presumably on account of home contact. School contact also may spread infection. Despite claims that a few epidemics have been due to water-borne or milk-borne infection, there is no conclusive evidence of such spread, and it has been excluded in many epidemics.

The field epidemiology has been thoroughly studied by Pickles (1939) whose use of the opportunities of a country practice has established many

[1] Received December 23, 1944.

important points. He puts the incubation period at 26 to 30 days, which slightly reduces the range of Booth's (1927) suggestion of 20 to 40 days. The common occurrence of serial infection in families with intervals of 20 to 40 days between cases suggests that the period of infectivity is short. Infection has been transmitted by cases eight days before and seven days after the appearance of symptoms, and the release of cases from isolation a fortnight after the onset of symptoms has proved to be safe. Transmission appears to be by droplet infection. Similar findings have been recorded by Dunlop (1935) and Newman (1942) in rural areas and Ford (1943) in the town of Wembley. Ford, however, concluded that although it was probable that the mode of infection was by droplets, the possibility of spread by faecal contamination of fingers had to be considered.

Epidemics of jaundice have frequently occurred in troops in war time. The outbreak during the American civil war has already been mentioned and the disease also affected German troops in France in 1870 and British and French troops in the Middle East in 1915–18. More recently German troops have been affected in Libya, Russia, and Norway, and large-scale epidemics have occurred among British troops in the Middle East in 1942, and there and in Sicily and Italy in 1943. In 1915–18 the Middle East epidemics were associated with enteric fevers and dysentery, and faecal transmission was thought to be the mode of spread. In the Middle East epidemic of 1942 Spooner (1944) noted the absence of 20 to 40 day intervals between cases in tank and vehicle crews which suggested that the disease was behaving differently from infective hepatitis in English villages. It seemed also that spread by droplets was unlikely because the disease did not spread from new arrivals in prisoner of war cages, among whom the disease was rife, to prisoners who had been in the cages for some months. Cameron (1943) thought that contact infection did not explain the epidemics and that the infective agent was widely dispersed among troops who succumbed up to six months later under conditions of physical stress. It has also been suggested that the disease is spread by blood-sucking insects.

There appeared therefore to be several points of difference between the epidemiological pattern of the disease causing jaundice among troops in the Middle East and that found in epidemics of infective hepatitis in England. An opportunity to collect information about these points occurred late in 1943 when some units of the British Army returned to Great Britain from the Mediterranean area with an epidemic of jaundice in progress among them. Four formations were affected—a Group of units (X), an Armoured Division (A), and two Infantry Divisions (B and C). The clinical features of the disease in men from these units were investigated by Wilson and compared with the findings in cases which occurred in home-based troops in 1943–4. Comparisons of haematological and biochemical findings were made by Miles and Pollock respectively. It is hoped that all the results will be published shortly. The clinical course and laboratory findings in the two groups of cases were so similar as to leave no doubt that the disease affecting

both groups was infective hepatitis. Epidemiological data collected from the units are compared in the present paper with findings in civilian and other military epidemics, and analysed to show what evidence there was of straggling or explosive epidemics, of spread by contact, and of the influence of precipitating factors.

Monthly Incidence in Large Formations

Most of the units of Group X and of A, B, and C Divisions had landed in Sicily early in July 1943 and remained there until their return to Great

TABLE I*a*

Monthly incidence of cases

July 1943 to March 1944

	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Total
Group X	2	4	16	30	28	19	22	6	3	130
A Division	10	9	14	40	15	8	7	10	7	120
B Division	—	4	9	23	59	51	12	5	—	163
C Division	1	8	16	50	81	67	38	7	5	273
Total	13	25	55	143	183	145	79	28	15	686

TABLE I*b*

Monthly incidence of cases in schools of a country town

May 1943 to February 1944

School	Number of children	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Total
A	302	2	4	8	9	17	20	22	2	1	4	89
B	260	—	3	8	5	18	7	2	1	—	—	44
C	179	—	—	1	1	2	4	4	5	1	1	19
D	50	—	—	—	—	2	2	—	—	—	—	4
Total	791	2	7	17	15	39	33	28	8	2	5	156

Britain. A few units were sent from Sicily to Italy and returned thence either directly or via Sicily or North Africa. The numbers of cases which had occurred before units arrived in Great Britain were obtained from returns made by A.D.M.S.s and R.M.O.s. These figures are somewhat lower than the true figures because in a few units no records were available and because no information could be obtained about cases evacuated to hospital before the diagnosis was made. Nevertheless, they give an idea of the rise of the epidemic which agreed with the impressions of A.D.M.S.s and M.O.s of field ambulances. Cases which occurred after arrival in Great Britain were notified by A.D.M.S.s and checked against hospital returns.

The monthly totals for all units together (Table I*a*) show an almost symmetrical rise and fall with the peak in November and a high incidence in October and December. The peak in A Division was in October, in Group X in October and November, and in B and C Divisions in November and December. An exact parallel can be found in civilian epidemics where the smooth curve for a group of schools in a town can be broken down into

a series of epidemics in different schools with peaks in different months (Table I*b*).

Weekly Incidence in Large Formations

Table II and Fig. 1 show differences in the course of the epidemics in Group X and B and C Divisions. The epidemic in Group X had no marked

TABLE II

Weekly cases of infective hepatitis

July 1943 to March 1944

		1st	2nd	3rd	4th	5th week	Total
Group X	July	—	—	1	1	—	2
	August	—	1	2	1		4
	September	4	2	1	9		16
	October	5	7	7	2	9	30
	November	11	6	7	4		28
	December	5	2	12	—		19
	January	4	6	4	5	3	22
	February	3	1	1	1		6
	March	2	—	1	—		3
							130
B Division	July	—	—	—	—	—	—
	August	1	2	1	—		4
	September	2	2	4	1		9
	October	3	5	7	4	4	23
	November	21	20	10	8		59
	December	12	19	18	2		51
	January	1	2	4	3	2	12
	February	2	2	1	—		5
	March	—	—	—	—		—
							163
C Division	July	—	—	—	1	—	1
	August	1	1	2	4		8
	September	3	8	1	4		16
	October	7	4	14	12	13	50
	November	22	15	28	16		81
	December	39	12	3	13		67
	January	14	9	9	2	4	38
	February	2	2	1	2		7
	March	—	—	1	4		5
							273

peak, but there was an appreciable rise in the incidence of hepatitis from September to January. The units in Group X had different itineraries and different battle experience in Sicily and Italy and arrived in Great Britain at different times. The epidemic lasted longer in units which broke their journey at Algiers than in those which came straight either from Sicily and arrived a fortnight earlier or from Italy and arrived early in 1944 (Table III). Ambulant cases, not included in the Tables, occurred during the fortnight spent in Algiers and were a possible source of infection for the cases which occurred in January. The epidemic in B Division began in October, a month after the troops moved into billets in Sicily. The incidence rose during that

month and reached a peak during the voyage and immediately after arrival in Great Britain. The number of cases in the next two weeks was less, but there was a sharp rise in the following two weeks. The men who fell ill then had been in close contact four weeks earlier with cases on board ship, where

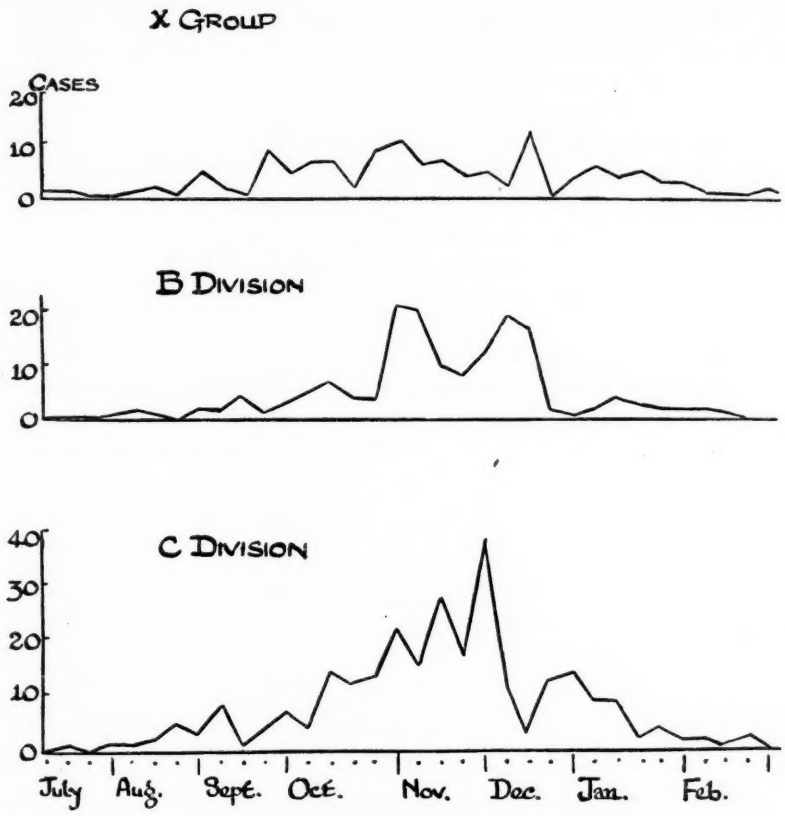

FIG. 1. Weekly incidence of infective hepatitis

troops were crowded together and upper respiratory infections were prevalent. In C Division the rise in the incidence of infective hepatitis began

TABLE III

Monthly cases in units of Group X known to have arrived in Great Britain on different dates

	1943						1944		
Arrived	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.
Late 1943, from Sicily	—	1	4	7	9	6	4	1	1
Late 1943, via Algiers	1	1	4	19	12	10	12	3	2
Early 1944, from Italy	—	—	—	—	3	—	—	2	—
	1	2	8	26	24	16	16	6	3

earlier, perhaps because the Division was quartered for a time in a monastery before moving into billets at the end of September. The rise continued until the voyage home. Thereafter the incidence fell fairly rapidly with only a slight rise a month after the peak on board ship. Several of the men who fell ill then gave a history of close contact on board ship with cases in their own or other units. The differences in the course of the epidemics in these formations appeared therefore to be related to differences in the times at which there were increased opportunities of contact spread in Sicily and during the voyage home.

Intervals between Successive Cases

By going over lists of cases with the unit medical officers and seeing some of the men who had had jaundice, it was possible to find a number of pairs and groups of cases in officers and men of the same platoon, office, billet, or mess. Contact had been fairly close and frequent between the members of the pairs and groups.

In B Division the numbers of days between the onset of illness in six pairs were 22, 27, 31, 32, 35, and 37. In C Division there were three pairs in one battalion (K of Table V) with intervals of 13, 20, and 24 days. Two other men had been exposed to two previous cases each and the intervals were 14 and 16 days for the one and 26 and 27 days for the other. In one company of Battalion Q there were two pairs with intervals of 29 and 30 days. In another company four men fell ill within 10 days, which suggested a common source of infection. A third company had four batches of cases at intervals. The first case was followed by two others 31 and 34 days later. There was an interval of 27 days before the next two cases, and five days later a third man fell ill, making the third batch. The fourth batch consisted of two cases occurring 21 and 25 days after the last case of the third batch. In Battalion S there were seven pairs and the intervals between them were 13, 24, 24, 30, 34, 34, and 42 days.

Some men volunteered the information that they had been in closer and more frequent contact with men who did not develop hepatitis than with the man to or from whom their infection had apparently been transmitted. An instance of the sort occurred in a group of officers. Two of them developed hepatitis during the voyage home and were confined to their cabins where each was crowded in with three other officers. None of the six cabin-mates fell ill, but another officer who occasionally visited the patients developed hepatitis a month after they did. This capricious spread of infective hepatitis need occasion no surprise, for other infectious diseases, including smallpox, provide many similar examples.

Further evidence of a 20 to 40 day interval between cases was provided by instances of infection in the families of men who fell ill while on leave, within a month of their return to Great Britain. An officer developed 'influenza' while on leave on 28.12.43. He apparently recovered, but on 3.1.44, three days after return to his unit, anorexia was noted. Dark urine

appeared on 4.1.44 and conjunctival icterus on 6.1.44. On 25.1.44 his wife developed 'influenza' and later became jaundiced. This was 26 days after her husband's last contact with her. There was no other known source of infection in the village where she lived. An officer of B Division fell ill while on leave on 23.11.43, his wife developed jaundice 26 days later (19.12.43), and his mother-in-law and sister-in-law became jaundiced on 3.1.44. A corporal developed jaundice while on leave on 23.11.43 and his

TABLE IV

Cases in Companies and Batteries in 10-day periods after initial case

Days	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	0 to 69
Cases	29	26	38	45	27	17	19	201
Percentage	14·4	12·9	18·9	22·4	13·4	8·5	9·5	100·0

wife fell ill with jaundice 32 days later. There were 33 secondary cases in these pairs and groups. Nine of them fell ill within 20 days of the onset in a previous case, and 24 between 21 and 41 days after it. The 20 to 40 day interval was therefore common enough in units in Sicily and soon after their return to Great Britain to suggest that case to case infection with the usual incubation period had occurred.

Another line of approach was to consider cases in companies and batteries where contact between individuals was likely to have occurred. Two hundred and one men were found to have fallen ill in a company or battery within 70 days of the initial case. Roughly 40 per cent. of these cases occurred between 20 and 39 days after the initial case as compared with 27 and 22 per cent. in the preceding and succeeding 20 days (Table IV).

These findings justify the conclusion that case to case contact played a part in the spread of infection. Field studies made during the epidemic might have produced more evidence in favour of contact spread for they could have included ambulant icteric and non-icteric cases and other jaundiced patients of whom no records were available. The general opinion among regimental medical officers was that there had been a considerable number of men with jaundice who did not report sick and that there were a few non-icteric cases. However, it was impossible to get satisfactory evidence about them or about the possibility that healthy carriers had been involved in the spread of infection. Admittedly there are apparently spontaneous cases of infective hepatitis during epidemics and sporadic cases in non-epidemic periods. For example, Wilson (personal communication) obtained no history of contact in 81 of 96 cases admitted to hospital from units based in Great Britain, and found that during the epidemic in the units which returned from the Mediterranean area nine of 44 cases admitted within a month of return had no known contact, and 30 of 42 cases admitted later had no known contact. However, sporadic and spontaneous cases are not uncommon in other infectious diseases in which the importance of contact spread cannot be denied. Contact with a previous case is

demonstrable sufficiently often in infective hepatitis to justify the conclusion that case to case contact plays a part in the spread of infection.

Monthly Incidence in Battalions and Regiments

In September 1943 there were cases in six battalions of C Division and only two battalions of B Division (Table V). This early diffusion of infection

TABLE V

Cases in units by months

	1943						1944			
Group X:	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Total	
Anti-tank Regt.	—	—	2	12	7	—	3	—	24	
L.A.A. „	1	1	3	—	—	1	—	—	6	
Field „	—	1	3	5	1	2	4	1	17	
Medium „ A	—	—	—	—	—	—	1	—	1	
„ „ B	—	—	—	—	—	1	3	—	4	
„ „ C	—	—	—	2	3	1	1	1	8	
„ „ D	1	1	—	2	2	4	3	1	14	
B Division:										
1 Bde. Battalion A	—	—	—	—	4	4	1	—	9	
„ „ B	—	—	—	—	2	—	—	—	2	14
„ „ C	—	—	—	—	—	—	3	—	3	
2 Bde. Battalion D	—	—	—	5	2	3	2	—	12	
„ „ E	—	—	—	—	1	1	—	—	2	23
„ „ F	—	1	3	2	1	2	—	—	9	
3 Bde. Battalion G	—	—	—	—	5	2	—	—	7	
„ „ H	?	?	?	2	10	6	1	—	19	53
„ „ I	—	—	2	4	4	11	6	—	27	
Field Regt. J	—	1	—	7	16	8	—	—	32	
C Division:										
1 Bde. Battalion K	—	—	4	8	—	2	1	—	15	
„ „ L	—	2	1	—	2	—	1	—	6	26
„ „ M	—	—	—	1	2	1	—	1	5	
2 Bde. Battalion N	?	?	?	?	?	3	1	—	4	
„ „ O	—	2	2	5	10	5	2	1	27	52
„ „ P	—	—	—	—	14	5	—	2	21	
3 Bde. Battalion Q	1	4	3	10	17	7	6	1	49	
„ „ R	—	—	1	2	8	5	—	—	16	82
„ „ S	—	—	1	6	1	3	6	—	17	
Field Regt. T	—	—	—	—	1	1	—	—	2	
„ „ U	—	—	2	4	4	3	1	—	14	
„ „ V	—	—	1	4	3	6	1	—	15	

throughout C Division was perhaps related to its concentration around a monastery at a time when the units of B Division were still scattered. Most battalions and regiments had a few cases every month for several months. The same type of incidence was found in 26 units of the Royal Air Force in North Africa in 1943. This straggling type of epidemic is found in many outbreaks of infective hepatitis and is typical of a mildly

infectious disease which is spread by contact and has a relatively long and varied incubation period.

In a few units more explosive outbreaks occurred. The Anti-tank Regiment of Group X had a short sharp outbreak in October and November. This regiment was never in action in Sicily and lived in bivouacs till November. They had more contacts with other units and with civilians after September when they moved to the neighbourhood of Messina. These contacts might have accounted for the October cases. The Field Regiment J of B Division moved into billets a month before their epidemic began. The explosive outbreak in Battalion P of C Division began six weeks after their move into billets. The more explosive outbreaks in some units therefore occurred a month or so after an increase in their contacts with other units and with the civilian population, which is the same interval as was found between the movements of the Divisions as a whole and the rise in their incidence of infective hepatitis. An apparently explosive outbreak occurred in a Field Ambulance after return to Great Britain. Nine cases were reported between 6 and 16 January 1944. Investigation showed that 13 cases occurred altogether, and that the weekly incidence from the week ending 18.12.43 was 1, 1, 1, 3, 5, 1, and 1 cases. The first patient developed symptoms while on leave. He returned to the unit on 21.12.43 and had few contacts, as most of the men were on leave and he was sent to hospital on the next day. The second case was a signaller attached to the unit. The most probable explanation of the January cases was that they had been infected in the unit before going on leave or on the troop train when they went on leave. In village outbreaks similar explosive outbursts occur and are at first sight suggestive of spread by some means other than contact. Investigation usually reveals that there have been cases of infective hepatitis in the village during the preceding month or months and that the probable explanation of the explosion is a spread from previous cases in school or at some social gathering. Spread by food, water, milk, or blood-sucking insects can be excluded with certainty. The occasional occurrence of explosive outbreaks in communities where infective hepatitis has been endemic does not therefore necessarily imply that infection has been spread by means other than contact.

Immunity and Variations in Incidence

The numbers of cases in the brigades of B and C Divisions varied from 14 to 82, and in their component battalions and field regiments from one to 49 (Table V). In individual companies and batteries there were up to 15 cases. Such variations in the incidence of infectious disease in groups of comparable size are common and cannot always be explained. However, certain observations suggested that the low incidence in some units was due to an immunity conferred by previous experience of an epidemic. During the 1942 epidemic, after the battle of Alamein, the Survey Regiment of Group X had 31 cases of which four were in regimental headquarters, one in A Battery, and 26 in

B Battery. Regimental headquarters and A Battery had previously had a series of cases of hepatitis. Their low incidence of hepatitis in 1942 was not due to lack of exposure, for they were in contact in the northern part of the Alamein line with Australian troops during the October peak of their epidemic. On the other hand B Battery had previously been in Iraq and Syria and had had no epidemic of hepatitis before joining the Regiment in July 1942. The Survey Regiment had only nine cases in 1943–4, which were evenly distributed among the Batteries. Apart from the arrival of B Battery in 1942 the composition of the unit had changed little since 1941. In B Division in 1943–4 there was a lower incidence in 1 and 2 Brigades (14 and 23 cases) than in 3 Brigade (53 cases). Brigades 1 and 2 had both experienced the 1942 epidemic in the Middle East, whereas 3 Brigade was stationed in Iraq during that winter and had no epidemic. The Field Regiment J had the highest number of cases in the Division and they had spent the 1942–3 winter in Malta and had had no epidemic. No data were obtained about replacements of casualties in the Division, but it appeared that during the 1943 epidemic the majority of men in 1 and 2 Brigades were men who had experienced the 1942 epidemic, while the men of 3 Brigade and the Field Regiment had not.

Civilian epidemics provide similar evidence. Pickles (1939) mentioned the long intervals between epidemics of infective hepatitis in Wensleydale, and Lisney (1944) noted that villages in Leicestershire which had had epidemics before 1942–3 were not affected by the widespread epidemic that winter. Both authors found that second attacks were rare; Pickles had none in about 1,000 cases and Lisney had four in 1,016 cases. These observations suggest that immunity is conferred by an attack of the disease, and probably by non-icteric attacks or subclinical infection. The same conclusion can be drawn from the lower incidence of the disease in adults than in school children. Second attacks appear to have been more common in troops in the Mediterranean area. Among 77 patients with hepatitis admitted to hospital in Great Britain in 1943–4 soon after their return from the Mediterranean area, there were three who had had jaundice five or more years earlier, and five who had had jaundice in the Middle East in the preceding three years. Among 82 patients who had never left Great Britain there was only one who had had jaundice before, and his first attack was eight months before his second, so that the possibility of a relapse has to be considered. The number of second attacks suggests that in the Mediterranean area immunity was broken down by larger doses of infection, or non-specific factors, or perhaps an immunologically distinct strain of virus.

It was possible to investigate the effect of exposure to a previous epidemic more closely in C Division. The three Brigades of the Division had all experienced the 1942 epidemic, but they had 26, 52, and 82 cases in 1943–4, as compared with 14 and 23 cases in 1 and 2 Brigades of B Division. It appeared that C Division had been less effectively immunized by the 1942 epidemic than 1 and 2 Brigades of B Division, but it was known that in

many units the replacement rate had been high so that many men in the units in 1943–4 had not in fact been exposed to the 1942 epidemic. Returns from 10 units showed (Table VI) that many cases had occurred in

TABLE VI

Cases in old and new troops

C Division

Unit	Old troops	New troops	Total
Battalion K	10	4	14
,, Q	18	24	42
,, R	10	6	16
,, S	5	11	16
Field Regt. U	8	6	14
,, ,, V	11	5	16
L.A.A. Regt.	12	10	22
M.G. Regt.	9	11	20
Anti-tank Regt.	2	4	6
R.A.S.C. Bde. Coy.	4	—	4
Total	89	81	170

'Old troops' had been with their unit during the epidemic of 1942.
'New troops' joined the units between May and September 1943.

TABLE VII

Infective hepatitis attack rates per 1,000

C Division

	Old troops	New troops	Whole unit
Battalion Q	49·3	84·2	64·7
,, R	26·2	22·2	24·6
,, S	30·0	23·0	24·6
Field Regt. V	18·3	50·0	22·8
Four Regts.	29·2	40·8	33·9

men who had been exposed to the 1942 epidemic. It was therefore necessary to calculate attack rates on men who had and had not been so exposed. The number of replacements in four units between May and September 1943 was taken as the number of 'new troops', because these men came from North Africa or Great Britain and had not been exposed to the 1942 epidemic. Subtraction of the number of 'new troops' from the average strength of the unit gave the number of 'old troops' who had been exposed to the 1942 epidemic. Attack rates were then calculated separately for old and new troops using the numbers of cases from Table VI. The rates (Table VII) are only approximate, but they do not show a consistently lower rate in old troops. In two units the rate was lower in old troops, but not significantly so, in one unit the rates were almost equal, and in the fourth the rate in old troops was higher. It was also noted (Table VIII) that there was no correspondence between the percentage of new troops and the attack rate of hepatitis in the four units, such as was to be expected if the old troops had been an immunized population and so reduced the threshold density of susceptibles.

There was therefore little evidence to show that men in C Division had been immunized by exposure to a previous epidemic, apart from the fact that the incidence in the Division was lower in 1943–4 than it had been in

TABLE VIII

Percentage of new troops and attack rate

		Per cent. new troops	Attack rates per 1,000
Battalion	S	73·8	24·6
,,	Q	43·8	64·7
,,	R	41·2	24·6
Field Regt.	V	14·3	22·8

1942, and lower than in the Central Mediterranean Forces and Canadian Troops in the Mediterranean area in 1943–4 (Table XI). It appears that any immunity conferred by previous exposure may be broken down by intensive dosage or other factors, and this idea was borne out by the observation that a number of men who had been exposed in the 1942 and 1943–4 epidemics and escaped the disease finally succumbed in England early in 1944. The part played in the reduction of incidence by previous exposure could be determined only by careful collection of data from suitable units and by an assessment at the same time of the possible effects of acclimatization and improved hygiene.

TABLE IX

Cases in officers and other ranks and ratios of attack rates

	1943						1944		
Group X:	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Total
Officers	1	1	6	5	3	3	2	—	21
Other ranks	1	3	10	25	25	16	20	3	103
Ratio	—	—	11·4	3·8	2·3	3·6	1·9	—	3·7
B Division:									
Officers	—	1	1	7	16	7	4	—	36
Other ranks	—	3	8	16	44	41	8	8	128
Ratio	—	—	—	10·0	8·3	3·8	—	—	6·6
C Division:									
Officers	—	3	4	13	21	12	4	1	58
Other ranks	1	5	12	37	60	55	34	6	210
Ratio	—	—	7·7	8·2	7·9	5·0	2·7	—	6·4

	1942				1943					
Y Division:	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May	Total
Officers	—	—	—	3	16	9	3	10	3	44
Other ranks	2	5	1	4	7	—	3	5	4	31
Ratio	—	—	—	11·9	52·0	—	26·2	50·5	9·9	42·1

The figures given for the ratio of attac' rates are the number of times the rate in officers was higher than that in other ranks. They were calculated on a ratio of officers to other ranks on the strength in Group X of 1 to 19, and in B and C Divisions of 1 to 23.

The ratios for Y Division were calculated from actual incidence per 1,000 on mean monthly strengths.

Higher Attack Rate in Officers than in Other Ranks

More striking than the variation of incidence in Units was the difference in incidence in officers and other ranks. Spooner (1944) reported that in the 1942 epidemic in the Middle East the incidence in officers was 4·7 times

TABLE X

Ratio of attack rates in officers and other ranks

Unit	Place	Year	Ratio of attack rates: Officers	Other ranks
Y Division	England	1942–3	42·1	1
B Division	Mediterranean and U.K.	1943–4	6·5	1
C Division	,, ,,	,,	6·4	1
8th Army	Mediterranean	1942	4·7	1
C Division	Mediterranean	1942	4·1	1
Group X	Mediterranean and U.K.	1943–4	3·7	1
Canadian Army	Mediterranean	Sept. 1943	2·9	1
	England	Nov. 1943	2·5	1
Royal Air Force	N. Africa	Oct. 1943	1·6	1
Static troops	England	1943	1·4	1
Canadian Army	Mediterranean	Nov. 1943	1·3	1

that in other ranks. In Group X and B and C Divisions the incidence in officers was higher than in other ranks throughout the epidemic and the difference decreased as the epidemic progressed (Table IX). The incidence in officers was markedly higher than in other ranks in an epidemic in Y Armoured Division in England where 44 officers and 31 other ranks were affected between September 1942 and May 1943. Figures for relative incidence in officers and other ranks gathered from many sources are summarized in Table X. The difference was small in the Royal Air Force in North Africa and in British and Canadian troops in England. It has been stated that in New Zealand troops in 1942 and in American troops in 1943, both in the Mediterranean area, the attack rate in officers was only slightly or not at all higher than in other ranks. The higher rate in officers has been found only in epidemics and is not always present even then, and it has been found in England as well as in the Mediterranean area. In the Royal Air Force in North Africa in October 1943 the attack rate in air-crews was 3·7 times that in ground staff and similar differences were found in other months. Possible explanations of these differences will be discussed later.

Higher Incidence in Troops in the Mediterranean Area

Monthly attack rates per 1,000 average strength were calculated for A, B, and C Divisions in 1943–4 (Table XI); the highest rates were respectively 2·5, 3·5, and 4·7. In 1942 and 1943 various bodies of troops in the Middle East had higher maxima ranging from 9·0 to 35·2 per 1,000, but in 1941 the maximum was 1·9 per 1,000. In static troops in England in 1943–4 there was a steady rate of 0·2 to 0·5 per 1,000. The difference between attack rates in the Mediterranean area and Great Britain is clearly shown by the

figures for Canadian Forces in the two theatres. Y Division during its epidemic in England had rates of 1·3 and 1·2 per 1,000 in January and April 1943. Attack rates during a civilian epidemic are included for comparison. The highest incidence among the 3,800 inhabitants of an East

TABLE XI

Monthly attack rates per 1,000

Place and troops	Year	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.
Mediterranean and Great Britain:										
A Division	1943–4	—	0·6	0·6	0·9	2·5	0·9	0·5	0·4	0·6
B Division	1943–4	—	0·0	0·2	0·5	1·4	3·5	3·0	0·6	0·3
C Division	1943–4	—	0·1	0·4	0·8	2·9	4·7	4·0	2·3	0·4
Mediterranean:										
Middle East Forces (U.K. and Dominion troops)	1941–2	—	0·3	0·9	1·2	1·5	1·9	1·0	1·0	0·5
	1942	—	0·1	0·5	0·6	4·1	5·4	9·0	—	—
New Zealand Forces	1942	—	—	—	—	35·2	—	—	—	—
8th Army	1942	—	—	—	—	—	—	15·0	—	—
C Division	1942–3	—	—	—	—	1·1	4·7	23·0	5·8	—
North Africa and Central Mediterranean Force	1943	0·2	1·0	1·5	2·4	8·9	9·3	8·9	—	—
R.A.F. in North Africa	1943	—	0·8	2·2	5·7	12·8	16·0	11·5	4·1	—
Canadian Forces	1943	—	—	0·8	8·5	16·9	14·4	11·6	—	—
Great Britain:										
Canadian Forces	1943–4	—	0·4	0·4	0·5	0·5	0·4	0·2	0·2	—
Eastern Command—										
District A	1943–4	0·4	0·2	0·3	0·5	0·3	0·3	0·4	0·3	—
District B—(static troops)	1943–4	0·2	0·2	0·2	0·2	0·3	0·2	0·3	0·5	—
Civilian epidemic:										
Town—all cases	1943–4	0·8	2·9	0·5	4·0	6·1	5·3	1·6	1·6	1·3
„ —school children	1943–4	8·7	21·0	12·4	32·2	54·5	40·9	11·2	3·7	6·2

		Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May
Y Division	1942–3	0·2	0·2	0·1	0·6	1·3	0·6	0·5	1·2	0·4

Suffolk town was 6·1 per 1,000, and in the children of school age 54·5 per 1,000. The low incidence in troops in England was the result of apparently sporadic cases and very occasional small epidemics in units. The higher incidence in the Mediterranean area was due to epidemics in many units, though sporadic cases also occurred. Cullinan (1943) found an intermediate picture in troops in Syria, mainly sporadic cases, but a fair number of epidemics.

Factors Responsible for a High Incidence

In discussing some of the factors which may have been responsible for the higher incidence in the Mediterranean area than in England, in officers than in other ranks, and in air-crews than in ground staff, it will be convenient to consider firstly the infective agent, secondly factors affecting susceptibility, and thirdly factors affecting the spread of the infective agent.

The infective agent. The higher incidence might have been due to a more 'pathogenic' strain of virus, in the sense that infection with it produced more overt cases. Alternatively, the strain might have been more 'infectious' so that infection was more widely spread and cases were then produced by environmental factors. Jaundice of unknown aetiology is endemic in the more densely populated parts of the Mediterranean littoral and mild cases in native children are thought to be the source of infection for adult newcomers such as troops in 1917–18 and 1942–3 and also (Kligler, Btesh, and Koch, 1944; Btesh, 1944) Jewish immigrants from Central Europe. Some evidence is now available to suggest that the 'Mediterranean virus' is not more pathogenic or infectious than other strains. Clinical and laboratory investigations of men who fell ill soon after their return to Great Britain showed that the disease was no more severe in them than in men who contracted it in Great Britain. In the autumn of 1943 it was noted that infection did not spread on aerodromes in Great Britain from men who developed hepatitis soon after returning from the Mediterranean area to men in close contact who had not been abroad. There was no outbreak in 1944 among many reinforcements drafted to the units which had returned from the Mediterranean, although cases continued to occur among men who had returned. Scrutiny of civilian cases of infective hepatitis notified to Medical Officers of Health in the first four months of 1944 showed that there were no fresh outbreaks in villages or towns where units had been stationed during their epidemics in December. In addition to the three cases of familial infection already mentioned there were 16 men who developed the disease while on leave and did not infect their families. Thus three of 19 families (16 per cent.) had more than one case. This is remarkably similar to the 17·5 per cent. of families with more than one case noted by Ford (1943) during a civilian epidemic in Wembley and suggests a similar pathogenicity and infectivity of the viruses.

Variations in pathogenicity and infectivity of the virus would not explain the higher attack rate in officers and air-crews, and it is improbable that they were responsible for the higher attack rate in the Mediterranean area. The presence of endemic foci of disease there may have contributed to the origin and scale of the epidemics, particularly if the strain concerned were immunologically different from those in other parts of the world. It is, however, worth while considering that the occurrence of as many cases of infective hepatitis among troops in the Mediterranean area as occurred sporadically among troops in Great Britain in 1943–4 would have provided abundant sources of infection.

It is desirable to draw attention to the observation that infective hepatitis may be epidemic in one group of people and yet may not spread to another group in close contact with them. Spooner's (1944) observations on prisoners of war in the Middle East have been mentioned and the observations made in England on aerodromes in 1943 and in East Anglia in 1944 are additional instances. In the last epidemic infection was transmitted to some family

contacts, so that the explanation of the absence of secondary epidemics most probably lies in some characteristics of the exposed group as a whole or of the individuals composing it. Speculation about these differences would be idle, but the phenomenon appears to be established, and in consequence it is necessary to exercise caution in accepting the absence of secondary epidemics in groups of persons exposed to cases of homologous serum hepatitis as an argument in favour of the view that homologous serum hepatitis and infective hepatitis are due to different agents.

Factors Increasing Susceptibility

Many officers and men who had been in the Mediterranean area suggested that one factor or another had been responsible for the epidemics of jaundice. An attempt was made to collect evidence about some of these factors.

Climate. A hot climate is said to predispose to disorders of the liver, but abuse of alcohol, dietary indiscretions, and intestinal diseases are cited as additional causative factors. The epidemics in the Mediterranean area have been seasonal, beginning in September or October and reaching a peak in November and December (Table XI) or January (Willcox, 1919). Thus they begin after the hottest month and have their peak in the cold season. A direct effect of hot climate can be excluded. Increasing cold at night coincides with the rise of epidemics of hepatitis and this factor has been credited with a greater effect upon officers who change into pyjamas than upon other ranks who do not. Chill during flying has been advanced as an explanation of the higher incidence in air-crews. The diurnal variations in the Western Desert are greater in the interior than on the coast, and in Sicily greater in the mountains than on the plains, but no data were available to show whether these differences affected the incidence of hepatitis. In the case of air-crews the effect of chill during flying would be a direct one, but in the Army the effect of cold nights might be exerted by an increase in contact spread owing to greater crowding in confined spaces.

Age. It has been suggested that the younger age of air-crews than ground staff might account for their greater incidence of hepatitis. In civilians the maximum incidence is in school children, though many young adults may

TABLE XII

Percentage of cases in age groups

Age group	Troops from Mediterranean	Troops in Eastern Command
18 to 19	—	15·9
20 to 24	37·5	32·1
25 to 29	35·3	22·8
30 to 35	19·1	13·9
35 to 39	5·8	12·0
40 and over	2·3	3·3
	100·0	100·0
Number of cases	173	308

be affected and no age is exempt. Selander (1939) has given age specific attack rates for Götland in 1929–32. In males aged 10 to 14 years the rate was 65·1 per 1,000, and in the seven five-year age groups from 15 to 49 the rates per 1,000 were 25·8, 35·9, 17·6, 27·4, 13·9, 15·8, and 7·9. The rate in the 20 to 24 age group was 35·9 per 1,000 which was higher than in older men, but not sufficiently so to account for the differences between air-crews and ground staff or officers and other ranks. Table XII gives the age distribution of cases of infective hepatitis in the troops who returned from the Mediterranean and in home-based troops. The differences are due at least in part to differences in the age distribution of the troops from which the cases came, but they do not suggest that the latter differences would explain the differences in attack rates.

Physical strain. Cameron (1943) suggested that an attack of infective hepatitis was frequently precipitated by physical strain. This factor might have played a part in producing the epidemic among New Zealand troops in October 1942, because the epidemic followed their hard fighting during the retreat to Alamein. In the units studied in the present paper the epidemic occurred several months after fighting in Sicily had ceased, and only 3 Brigade of Division B showed a possible effect of physical strain in that they fought in Italy during September and had a higher incidence than 1 and 2 Brigades of the same Division which did not leave Sicily. In Y Division the April peak followed a month after a strenuous exercise, but no such explanation could be found for the January peak. In C Division in 1942 the incidence was higher among officers with office jobs than among those exposed to physical strain. In 1943 in Group X the highest incidence was in the Anti-tank Regiment which was never in action, and the incidence was as high in base troops in North Africa as in troops in Sicily and Italy. Physical strain was therefore not a precipitating factor in many of the outbreaks studied. Data from other epidemics might show that it had some effect.

Diet. Some officers stated that they lost weight during the advance after the Alamein break-through owing to loss of appetite and a monotonous diet. This experience was not universal, and published accounts of the Middle East Force ration scale (Gear, 1944) do not suggest that deficient diet can have been an important factor. Water supplies were sometimes low and disturbances of water balance may have affected susceptibility. In Sicily 'compo' rations were used during fighting, and field rations later. Fruit and vitamin preparations were available during the Middle East and Sicilian campaigns. It does not appear that dietary deficiency was a cause of the high incidence of hepatitis.

Alcohol. Alcohol may precipitate a relapse of hepatitis during convalescence, but the general impression among medical officers was that differences in alcohol consumption did not account for the higher attack rates in the Mediterranean area in officers and air-crews. Teetotallers were affected and the proportion of 'more than average' and 'moderate' drinkers

among cases was much the same as among those who did not develop the disease.

Other diseases. In 1917–18 the curve of infective hepatitis incidence followed a month after the dysentery curve, which suggested some connexion

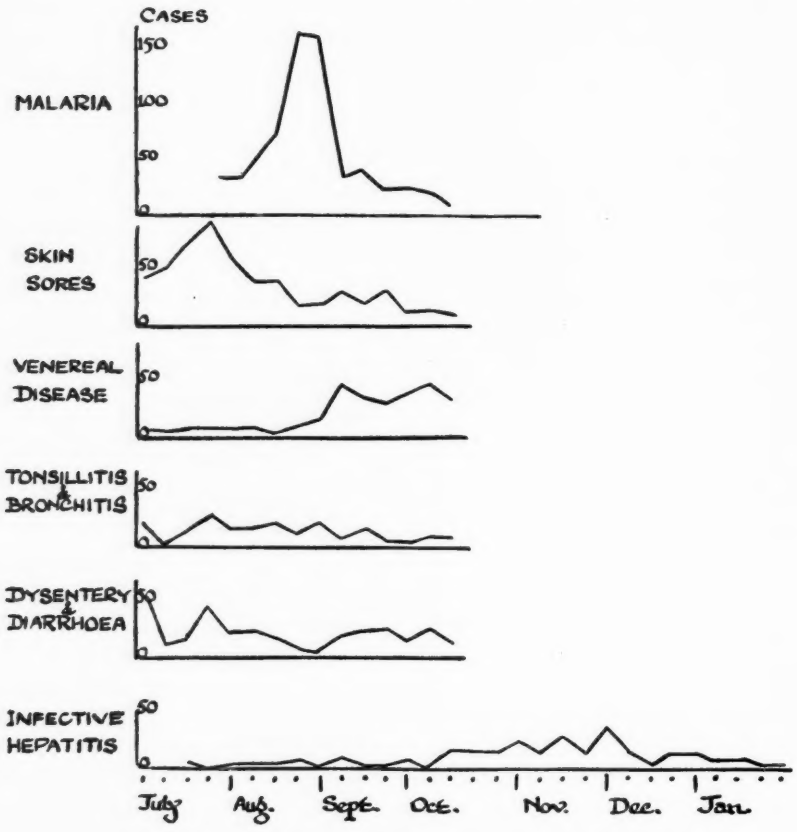

FIG. 2. Weekly incidence of certain complaints in C Division.

between the two conditions. In 1943 there was a three months' interval between the two curves so that the connexion did not appear to be so close. Several other diseases have been suggested as associates of infective hepatitis, and an opportunity to examine this possibility was afforded by the A.D.M.S. of C Division who provided a graph of the incidence of certain complaints during the Sicilian campaign (Fig. 2). In September and October, before and during the rise in incidence of infective hepatitis, skin sores and upper respiratory infections decreased, diarrhoea and dysentery increased slightly, and venereal disease increased markedly. There was a large rise in malaria in late August, but this rise and a second rise in the spring of 1944 were not accompanied by a rise in the incidence of infective hepatitis. There was

nothing in the incidence of these complaints which suggested that in C Division any of them had precipitated the outbreak of hepatitis. Relationships between infective hepatitis and other diseases have been postulated usually in the presence of concurrent epidemics, and the most likely explanation seems to be that the conditions which favoured the spread of the other infection also favoured the spread of infective hepatitis.

The Method of Spread of Infection

It is convenient to pass from the discussion of the possibility that malaria may be a precipitating factor to a consideration of the suggestion that infective hepatitis is spread by blood-sucking insects. Voegt (1942), Cameron (1943), and MacCallum and Bradley (1944) have shown by human transmission that the blood of infective hepatitis patients may be icterogenic, and it is now recognized that homologous serum hepatitis may follow about three months after transfusion or inoculation with human serum or plasma (Memorandum, 1943). Further, doses of 0·1 c.c. of serum have been icterogenic (Bradley, Loutit, and Maunsell, 1944). It is therefore a possibility that blood-sucking insects might transmit infection, leaving aside for the present the unsettled question of the identity or difference of homologous serum hepatitis and infective hepatitis.

In C Division there was an interval of about three months between the August peak of malaria and the November peak of infective hepatitis. Also

TABLE XIII

Incidence of malaria (August) and infective hepatitis (July to January) in nine Battalions

Malaria incidence in unit	Number of hepatitis cases	Average
High	15, 17, 49	27
Medium	5, 16, 21	14
Low	4, 6, 27	12·3

there was in the nine battalions some correlation between the incidence of malaria in August and the subsequent incidence of hepatitis (Table XIII). However, there have been many epidemics of hepatitis, including the 1942 epidemic after the battle of Alamein, in which blood-sucking insects could not have been concerned. The epidemiological pattern of the outbreak in Sicily was very similar to that in epidemics in which spread was by contact and there was at least some evidence that contact spread played a part in Sicily. The evidence does not therefore justify the conclusion that insect transmission was concerned, and serious consideration of the idea can be postponed until more convincing evidence is obtained.

Spread by eating utensils has been suggested because the higher incidence in officers might be explained by their use of communal dishes which are washed together, whereas other ranks have their own utensils and wash them themselves. Some data have been put forward to support the idea (Witts, 1944), but the verdict here again is still 'not proven'.

The orthodox belief that infective hepatitis is spread by droplets from the respiratory tract is supported by the autumn–winter incidence of the disease in Sweden (Selander, 1939), Great Britain (Cullinan, 1939), and the Mediterranean area (Cameron, 1943; Cullinan, 1943; Kligler, Btesh, and Koch, 1944; Willcox, 1919; Table XI), and also by the apparent transmission of the disease by casual contact (Newman, 1942). Additional evidence in favour of this mode of spread is the association of a high incidence of infective hepatitis with concurrent epidemics of upper respiratory infection (for example, the colds in the troopships of B Division; measles, McFarlan, 1941; stomatitis, Cookson, 1944). Findlay and Martin (1943) reported the transmission of what they believed to be homologous serum hepatitis by nasopharyngeal washings, but MacCallum and Bradley (1944) had only doubtful success with similar material from infective hepatitis cases. The latter authors transmitted infective hepatitis with an ether-treated suspension of faeces sprayed into the nose and pharynx. The association of jaundice in the Mediterranean epidemic of 1917–18 with enteric fevers and dysentery has already been mentioned, and there have recently been more reports of the association of intestinal infections with infective hepatitis (dysentery, Thorne and Estabrook, 1941; diarrhoea and vomiting, Sudds, 1944). The 'indescribable filth' and 'plague of flies' in the Alamein line and the constant inspiration and ingestion of the all pervading dust were features of the life of troops in 1942 which suggested that faeces, flies, and dust might have played a part in the spread of infection. Lack of water and of washing facilities also increased the risk of spread by fingers contaminated by droplets or faeces.

The available evidence suggests that contact is the mode of spread of infective hepatitis. There is no reason why droplets and faeces should not both be infectious, and their relative importance in the spread of infection may vary with different living conditions. The higher incidence in the Mediterranean area and in officers may be to a great extent the result of increased opportunities of contact spread. Other factors are doubtless concerned, for epidemics of infective hepatitis, as of other infectious diseases, may result from different combinations of various factors. Epidemiological investigation during an epidemic is the only means of discovering the important factors in a particular epidemic and so suggesting rational methods of control.

The results of investigations reported in the present paper demonstrate the difficulties of obtaining answers to the questions posed by Witts (1944). They are published in the hope of stimulating others to obtain better data which may give more conclusive answers.

Summary

1. Epidemics of infective hepatitis began in some units of the British Army in the autumn of 1943 while they were in Sicily and continued after their return to Great Britain later in the year or early in 1944.

2. The epidemiological pattern of the outbreaks was very similar to that of civilian epidemics. Numerous instances of 20 to 40 day intervals between the onset of illness in contacts were found in the units just as they are in families during civilian epidemics. The conclusion is drawn that these were instances of contact spread from case to case with a 20 to 40 day incubation period.

3. The lower incidence in some units might have been due in part to an immunity conferred by previous exposure to an epidemic.

4. In these and other epidemics the attack rate in officers was higher than in other ranks, and the attack rate in troops in the Mediterranean area was higher than in troops in Great Britain.

5. The presence of endemic foci of infective hepatitis in Mediterranean countries may be in part responsible for the high incidence in troops there. Some evidence is presented that the 'Mediterranean strain' of the infective agent is not more pathogenic or infective than other strains. Several instances are recorded of the failure of infective hepatitis to spread from one group in which it was epidemic to other groups with which the affected group was in close contact.

6. Chill, age, physical strain, diet, alcohol, and other infectious diseases did not play a major part in the causation of the epidemics, but their possible importance in other epidemics cannot be excluded.

7. Increased opportunities for the spread of infection either by droplets or from faeces are associated with many epidemics, and it is probable that they explain at least in part the higher incidence in the Mediterranean area and in officers.

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SPINAL OSTEOPOROSIS OF UNKNOWN ORIGIN[1]

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With Plates 7 to 9

A PAINFUL condition of the spine of old people was described in 1863 by Charcot and Vulpian (1890) under the title 'Sur l'osteomalacie sénile'. This condition was probably what is now called hunger osteomalacia, which was seen in almost epidemic form in Vienna after the war of 1914–18 (Cramer and Schiff, 1920; Dalyell and Chick, 1921; Hume and Nirenstein, 1921). Another condition which causes great pain in the back without any general symptoms has been called spinal osteomalacia, and more recently spinal osteoporosis, either senile or presenile. This has been confused with hunger osteomalacia, and it is not always possible to distinguish in the published descriptions which disease was meant. Since the beginning of 1938, five series of cases have been described (Lance, Girard, and Lance, 1938; Ravault, Graber-Duvernay, and Léger, 1939; Meulengracht, 1939; Black, Ghormley, and Camp, 1941). The morbid anatomy and the mechanism of production of the spinal deformity were worked out by Schmorl (Beadle, 1931; Schmorl, 1932). In this country the condition has not been described apart from the communication of Morris at the meeting of the Association of Physicians in 1943 (Morris, 1943). The clinical condition of 20 patients and the necropsy findings in two are recorded in the present paper. The dietary difficulties during the present war give the subject special interest, as no less than 17 of the patients were seen between September 1939 and 1943.

Clinical Features

Age and sex. The ages in four series of cases (Lance, Girard, and Lance, 1938; Ravault, Graber-Duvernay and Léger, 1939; Meulengracht, 1939; Burrows and Graham, 1945), amounting to 53 in all, are set out in Table I, which gives also the ages at the time of onset of symptoms in our own cases. Fig. 1 gives the number of cases in each decennium (A) and quinquennium (B). The decennial chart (A) shows a peak of incidence at the 60 to 70 decade, which is shown by the quinquennial chart (B) to be due to the high number of patients between 60 and 65 years of age. The relatively high incidence between 55 and 80 years is mainly due to female patients; the main incidence in men is between 40 and 70 years. We do not know the reason for

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the different age incidence in men and women. It is curious that the female cases are so few before the menopause, when menstruation, pregnancy, and lactation are taking their tribute of calcium, but in any event frank cases of puerperal osteomalacia would be excluded from the figures. The onset of

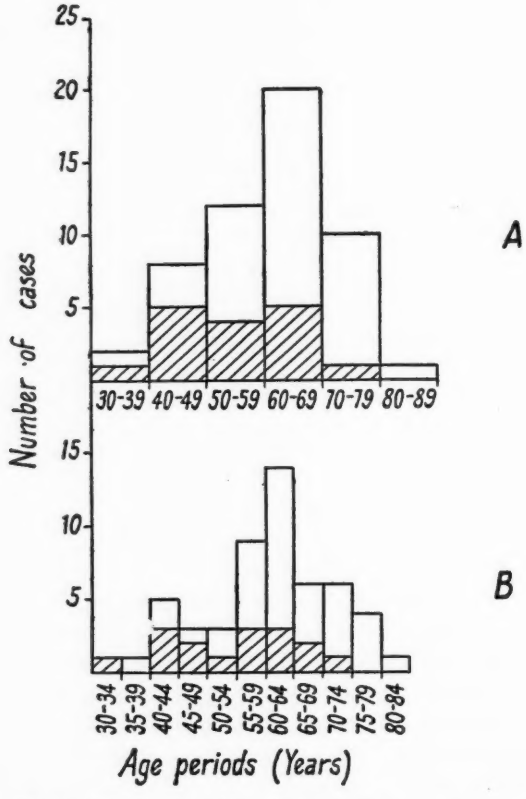

FIG. 1. Diagram to show the number of patients, taken from the same 53, in each decennium (A) and quinquennium (B). Male patients are represented by cross-hatching.

symptoms in one of our cases was precipitated by pregnancy. Of the 53 patients, 16 (34·5 per cent.) were men and 37 (65·5 per cent.) women. Among 208 patients aged 45 to 87 years (average 62 years) diagnosed at the Mayo Clinic as suffering from senile osteoporosis of the spine, Black, Ghormley, and Camp (1941) found 41 men and 167 women. Albright, Smith, and Richardson (1941) found only two men among 42 patients aged less than 65 years, suffering from non-localized osteoporosis. A glance at Table I and Fig. 1 shows how misleading are the names senile or presenile osteoporosis.

Constitution and temperament. Most of our patients have been unusually spare; two women were abnormally fat, and the radiographic difficulties of

displaying rarefied bone were consequently accentuated. The fussy, over-anxious type of patient was frequent.

Symptoms. There may be no symptoms referable to the spinal condition, which may be found by chance in the investigation of a case of gastro-

TABLE I

The ages of the patients in four series of cases, comprising 53 in all and including those forming the basis of the present paper. In this instance the ages and the times of onset are also given

	Authors				
	Lance, Girard, and Lance (1938)	Ravault, Graber-Duvernay, and Léger (1939)	Meulengracht (1939)	Burrows and Graham (1945)	
	Number of cases				
	6	8	19	20	
	Patients' ages in years	Patients' ages in years	Patients' ages in years	Patients' ages in years	Ages in years at onset of symptoms
	56	41	41	32	32
	57	53	42	38	26
	59	63	47	44	44
	60	72	49	44	39
	60	72	57	49	45
	62	76	59	50	50
	—	77	59	53	50
	—	83	62	56	55
	—	—	62	58	56
	—	—	63	59	59
	—	—	64	61	61
	—	—	64	61	61
	—	—	64	63	61
	—	—	69	64	64
	—	—	71	67	27
	—	—	71	67	61
	—	—	72	67	63
	—	—	77	68	68
	—	—	78	69	64
	—	—	—	72	72
Mean	59	67·1	61·6	57·1	52·9
Median	59·5	72	63	60	57·5

Mean age of 53 patients in combined series = 60·5 years
Median „ „ „ = 62 „

intestinal disturbance. The local symptoms, if present, may be acute or chronic. Sometimes acute symptoms supervene on chronic. Acute symptoms occurred in 11 of our patients, in eight as the first complaint; sometimes there was more than one attack. The patient, while performing some trivial movement, was seized with agonizing, sometimes nauseating, pain in the lumbar or lower dorsal region; she might not only cry out but continue to do so. One of our patients heard something crack in her back. Another felt an inaudible 'snap, like an elastic band breaking' in the lumbo-dorsal region.

Yet another 'felt something give as though something in the back had collapsed'. Two of Meulengracht's (1938, 1939) patients also thought that they felt something break, and one of them stated that he had heard the bone break. The patient might or might not fall, but was usually put to bed, and remained there for a matter of days or weeks, at first unable, and later afraid, to move his back. Nothing seemed to give relief except heat and rest. Almost certainly the acute symptoms mean collapse of a vertebral body. It might be expected that a flexion movement would be the exciting cause, because it is flexion injuries that lead to crush fractures of normal vertebral bodies. In our cases the history usually suggested extension of the flexed spine as the cause, the pain coming on during the act of lifting a weight, opening a stiff drawer, or 'stretching' on waking in the morning. A flexion movement appeared to start an acute attack in two of our patients; one, who had suffered previously, was applying a spinal support prone, and flexing her spine to allow the abdominal straps to be buckled, when she was suddenly stricken; the other was in the act of bending down. Moffat (1934) had a similar case. Coughing started the severe pain for the first time in one case. The predominant chronic symptom is backache which comes on gradually. It is usually situated in the lumbar region, but is sometimes thoracic. It is nearly always worse with activity and is relieved by rest. It may recur on the first resumption of activity after rest. Sneezing or coughing may aggravate the pain. Sometimes the back feels weak and exceptionally there may be stiffness. The pain sometimes radiates to the front of the chest, the abdomen, or the buttocks and the backs of the thighs. Some patients, whose histories were described by other authors, complained that they were becoming shortened and bowed, but only one of our patients made this complaint. Although tetany did not occur, complaint of paraesthesiae in the feet and legs was made by one patient, and in the hands and feet by another (Meulengracht, 1938, 1939). One of our patients had paraesthesiae in the feet and legs with loss of vibration sense in the tibiae.

Signs. The principal physical sign, which has been present in all our cases, is kyphosis or less commonly kypho-scoliosis. The kyphosis involves a substantial number of vertebrae and is therefore of the rounded variety and not angular, although some spinous processes may be more prominent than their neighbours. At the stage in which our cases were seen, the kyphosis was usually almost restricted to the dorsal or lower dorsal region. Although the lumbar region may show bowing or loss of its normal curve, more often this is fairly well preserved and sometimes it is even exaggerated to form a lordosis, presumably compensatory in character. The mobility of the lumbo-dorsal spine may be preserved in quite advanced cases, failing a vertebral collapse, but is as a rule substantially diminished and may be trivial. Previous writers have described clinical signs dependent on telescoping of the lumbar spine and the approximation of the costal margin to the iliac crests, namely shortening of the lumbar region, oblique folds running downwards and outwards in the dorso-lumbar region, and a deep transverse

abdominal furrow. These may all be present. Tenderness of the spinous processes on palpation or percussion has been described (Ravault, Graber-Duvernay, and Léger, 1939).

Radiological Changes

Osteoporosis. Osteoporosis of the lumbar and lower thoracic vertebrae may be extreme, and Meulengracht (1939) has pointed out that the consequent difficulty in securing good radiographs is characteristic of the condition. If the bony texture is apparent it seems coarser than the normal, but more often it is not discernible, and the vertebral bodies are said to have the appearance of ground glass. Sometimes, only their outline can be made out. The cervical spine may be quite unaffected or show slight porosis. The pelvis often shows some porosis, but shows no appreciable deformity. The ribs, clavicles, sternum, and scapulae may sometimes be involved. A control radiograph of the hand often provides evidence of generalized osteoporosis, but this is much less pronounced than the condition of the lumbar and dorsal vertebrae would suggest, and is frequently not demonstrable at all, since the osteoporosis is not uniform throughout the body. Its distribution is extremely interesting. It seems possible that the lower vertebrae, with their large masses of well-vascularized cancellous bone, have a special function as a reservoir in the maintenance of the blood-calcium at an almost constant level. Hunter (1930) has cited evidence that the spongiosa acts as the storehouse of readily available calcium, and that the corticalis is at first spared in the process of calcium mobilization. It is noteworthy also that in the normal adult red marrow is almost confined to the bones of the spine, limb girdles, and thoracic cage. These bones are consequently highly vascular, and therefore provide a more elastic store of calcium than the bones containing fatty marrow, which has a relatively poor blood supply.

Bi-concavity of the vertebral bodies. The upper and lower surfaces of the vertebral bodies become concave, and the intervertebral disks become bi-convex and often thickened (Plate 7, Figs. 3 and 4). The change is confined to that part of the spine showing gross osteoporosis. The extent of deformity varies greatly between patient and patient, and often between adjacent vertebrae in the same patient. The main part of the upper or lower surface of each vertebral body is separated by a hyaline cartilage plate from the rest of the intervertebral disk. Rather illogically, the cartilage plate is regarded, not as part of the vertebral body, but as part of the disk. The remainder of this is composed of the highly elastic nucleus pulposus enclosed in the tough annulus lamellosus. The cancellous bone of the vertebral body extends almost to the cartilage plate with a poorly developed intervening cortical layer. Softening of the cancellous bone by osteoporosis allows the cartilage plate to be indented seemingly by the pressure of the turgid nucleus pulposus; the pressure depends upon superimposed weight and muscle pull, and consequently alters with spinal movements. Often the bone

appears to resist the pressure by a subchondral increase, or relative increase, in density (Plate 7, Fig. 4). The indentation of almost the whole surface in these cases should be distinguished from the more localized Schmorl's node, which results from the herniation of the nucleus pulposus through a defect in the cartilage plate and so constitutes an actual incursion of nuclear substance into the bone. This may occur in osteoporosis, but is not characteristic of it. A wholly false appearance of bi-concavity may be found in those vertebrae which are not accurately centred on the film, but recognition is easy if the possibility is appreciated.

Collapse of vertebral bodies. Uniform wedging. This is the commonest form of collapse. A bi-concave vertebra becomes narrowed in its anterior part, so that the vertebral body becomes wedge-shaped as well as bi-concave. The apex of the wedge is usually forward, though lateral angulation also may occur. This type of wedging, without radiological evidence of fracture and without acute symptoms, seems to be of gradual development over a matter of weeks.

Generalized crushing. Wedging of a vertebra may be accompanied by acute symptoms and may be associated with evidence of fracture in the form of cortical buckling. Here we are concerned with a pathological crush fracture.

Localized fracture. A small part only of the vertebral body may be affected. Collapsed vertebrae, as distinct from merely compressed vertebrae, have been found in 14 of our cases, as follows: T_8 alone (twice), L_1 alone (twice), L_3 alone, L_1 and L_3, T_6 and L_1, T_7, T_8 and T_9, T_7 and T_{12}, T_8 and T_{11}, T_{11} and T_{12}, T_5, T_6 and L_1, T_{12}, L_1 and L_5, T_6, T_9, L_1 and L_5. Traumatic fracture commonly affects L_1 or T_{12}, but is uncommon in thoracic vertebrae above the twelfth. Often there is great variety of vertebral shape in the same spine.

Pseudarthroses between lumbar spinous processes. Meulengracht (1938) observed in several of his cases 'osteoarthrosis of the spinous processes', consisting of articulation of neighbouring spinous processes and the consequent development of pressure facets upon them, or, in other words, pseudarthroses between the spinous processes, 'kissing spines' as they have been called. This condition, which Meulengracht calls Baastrup's disease, was described by Brailsford (1928); it was elaborated by Baastrup (1936) as a possible cause of lumbago. Meulengracht considers the changes to be secondary to the vertebral collapse, and that they may constitute an independent source of pain. Lumbar spinous processes have approached one another in some of our cases; the progress of the lesion is well shown in Plate 7, Figs. 5*a* and 5*b*. The changes are interesting as evidence of telescoping. This signifies softening and collapse of the neural arches as well as the bodies of the vertebrae; affection of the bodies alone causes kyphosis, not telescoping. The signs found when lumbar telescoping occurs, shortening of the lumbar spine with the formation of cutaneous folds, have already been described.

The radiological appearances are identical with those of osteomalacia.

Aetiology

Diet. Estimates were made of some of the more important constituents of the usual diet of 16 of our patients, and are shown in Table II. These must be accepted with reserve, because they depend on information imparted by patients and because of the variation in the composition of foodstuffs.

TABLE II

Estimates of certain minerals and vitamins in the habitual diets of some patients with osteoporosis of the spine of unknown origin

Patient	Sex	Age	Calcium mg.	Phosphorus mg.	Ca/P ratio	Vitamin A i.u.	Vitamin C mg.	Vitamin D i.u.
W. S.	F.	38	1,407	—	—	1,447	29	144
E. P.	F.	44	200	689	(1 : 3·44)	—	—	Low
L. L.	F.	49	520	890	(1 : 1·71)	About 1,000	About 100	25
E. D.	F.	50	Low	735	—	—	—	—
M. S.	F.	56	< 100	278	(> 1 : 2·78)	—	—	Low
J. F.	F.	59	697	713	(1 : 1·02)	1,500	69	16
J. P.	F.	61	1,200	1,011·2	(1 : 0·84)	—	—	Low
M. E.	F.	63	419	678·4	(1 : 1·64)	3,026	48	36
K. M.	F.	67	400	531·7	(1 : 1·33)	—	—	Moderate
M. M.	F.	67	750	909	(1 : 1·2)	—	—	Low
B. J.	F.	68	591	626	(1 : 1·06)	2,900	14	76
R. H.	M.	44	1,200	—	—	—	—	—
H. P.	M.	53	270	553·5	(1 : 2·05)	—	—	Moderate
H. H.	M.	58	595	970	(1 : 1·63)	3,960	28	68
F. S.	M.	61	120	613 (?)	—	—	—	—
F. K.	M.	69	713	985	(1 : 1·38)	3,488	38	41
'Standard requirement'			550	1,067	1 : 1·94	3,000 to 4,000	25 to 50	(?) 300 to 600

The question of the amount of calcium which the diet should contain is not yet settled. Sherman (1920) considered that 450 mg. daily was the minimum and that a 50 per cent. increase to 675 mg. would be sufficient. Leitch (1936) investigated 397 women and found that 318 were in a negative balance with diets which varied from 150 to 200 mg. to 700 to 750 mg. daily. She found that with a diet of 550 mg. the numbers of positive and negative balances were equal, and she suggested this figure as the true maintenance requirement. The fact that 45 women were in negative balance on diets varying from 500 to 700 mg. and that 39 women were in positive balance on diets varying from 150 to 450 mg. shows that other factors besides the amount of calcium in the diet help to determine whether a patient is in negative or positive balance. If Leitch's figure of 550 mg. is taken, it is found that seven out of 16 of our patients were taking deficient diets, 270 mg. daily or less in four or five instances. Eight were presumably taking plenty of calcium, three of them taking a calculated amount of more than 1,000 mg. a day (Table II).

The daily phosphorus requirement is also uncertain. Sherman gives a figure as high as 1,320 mg. If we use Leitch's estimate for calcium and accept Sherman's hypothesis that the calcium and phosphorus should be present in the proportion of 1 : 1·94, we arrive at the figure of 1,067 mg.

daily. On this basis (possibly too high) the phosphorus intake was deficient in all 14 patients in whom it was investigated (Table II). By contrast, a patient with leukaemia mimicking clinically and radiologically other cases of osteoporosis of the spine had a daily phosphorus intake of 1,382 mg. Other figures for this case were calcium 991 mg., vitamin A 3,596 i.u., ascorbic acid 10 mg., and vitamin D, 63 i.u.

The intake of vitamin D appeared low in our patients, but here again we are handicapped by ignorance of the requirements of the non-pregnant,

TABLE III

Estimated maximum and minimum daily intake of calcium and phosphorus under conditions of food rationing, 1941–3

	Calcium mg.		Phosphorus mg.	
	Minimum	Maximum	Minimum	Maximum
From rationed food	171·5	423·6	310·5	493·9
From unrationed food (no added calcium)	164·4	164·4	279·8	279·8
Total without added calcium	335·9	588	590·3	773·7
From 10 oz., national bread with added calcium	171	171	—	—
Total	506·9	759	590·3	773·7
'Standard requirement'	*550*		*1,067*	

non-lactating adult. A further complication is the power of the individual to make vitamin D when exposed to sunlight. Many of our patients were elderly, and such often avoid direct sunlight.

The reason for an unsuitable diet has been sometimes a solitary life, sometimes eccentricity, and sometimes indigestion, histories of which were obtained in six of our patients. In at least one of these instances the diet appears to have been medically prescribed. Another case associated with a deficient diet taken for peptic ulceration was published by Ravault, Graber-Duvernay and Léger (1939). Mellanby (1932) has seen two childless women in this country with osteomalacia produced by dietary restriction medically advised. Similar cases have been reported by Decourt (1935), Weissenbach and Lièvre (1935), Loubeyre and Blondeau (1935), Black, Ghormley, and Camp (1941), and Schultzer (1933).

The possible effect of food rationing should be considered as 17 of the 20 cases had become manifest since the outbreak of the present war. Our dietitian, Mrs. Newman, has therefore calculated the amount of calcium and phosphorus which patients would have if they ate their full diet. The amount of calcium which was calculated to be available in the rationed foods during 1941 to 1943 was 172 mg. daily as the minimal figure and 424 mg. as the maximal figure when both the milk and cheese rations were at their highest. If the usual amounts of the unrationed foods containing calcium (herring, cabbage, dried milk) were eaten, an additional 164 mg. daily were probably taken, making 336 mg. as a minimum and 588 mg. as

a maximum. The total calcium of the diet has recently been increased by the addition of calcium to the national bread, so that a patient eating 10 oz. of bread daily takes an additional 171 mg. of calcium daily, bringing the minimal and maximal totals to 507 and 759 mg. respectively. It is doubtful, however, how much of the calcium added to the national bread will be absorbed, because national bread contains more phytic acid than white bread. McCance and Widdowson (1942) have shown that the subjects of their experiments all lost much more calcium when they ate brown bread instead of white bread, and the high loss was improved unexpectedly little by the addition of 200 i.u. of vitamin D to the diet. If the calcium in the bread is neglected, the figures 336 and 588 mg. represent the estimated limits of daily calcium intake in a subject who consumes the whole of his ration and an average amount of unrationed calcium-containing foods. The minimal figure is substantially lower than Leitch's estimate of the standard requirement, namely 550 mg. daily. Similarly, the phosphorus figures for the rationed foods gave a minimum of 311 mg. and a maximum of 494 mg.; with the addition of 280 mg. for the same unrationed foods, the figures become 590 as a minimum and 774 as a maximum. The phosphorus content of the war diet is very deficient, as judged by some standards, and may play an important part in causing osteoporosis if the deficiency is long continued. Although the war-time rationed diet may have contributed, and may have precipitated symptoms, it is probable that the greatest dietetic factor in our cases has been the exercise of individual preferences over many years before the war.

Habitual purgation. Most of our patients have indulged very moderately, if at all, but the following exceptions are noteworthy: (*a*) 'Carter's little liver pills' daily for 15 years, and, for the last three years, an alkaline powder as well; (*b*) Epsom salts daily for 11 years; (*c*) a phenolphthalein preparation daily for seven years; (*d*) liquorice powder twice a week for 43 years. These purgatives are hardly powerful enough to produce the liquid stools which might be responsible for an important loss of calcium. Purgation, if a factor at all in these cases, was almost certainly a minor one, but Meulengracht (1938) believed that it was an important or, perhaps, the only factor in some. The perversion in these cases was extreme and of long standing: (*a*) 1 to 1½ gm. of rhubarb root nightly for 40 years; (*b*) five senna pods nightly for 15 to 20 years; and (*c*) Carlsbad salts daily for 35 years. In the last instance he thought it probable that some of the calcium of the food was evacuated as insoluble calcium sulphate. As Meulengracht pointed out, the intestinal changes caused by abuse of laxatives may well tilt the balance when the constitution of the food is not optimal.

Alkalies. It has been supposed that alkalies, taken to excess, may impair the absorption of calcium and vitamin D by raising the pH of the gastric juice, and so precipitating dissolved calcium and also combining with calcium. This may be true, but the effect is probably unimportant unless the supply of calcium, phosphoros, and vitamin D is already meagre. Graham and

Oakley (1938) secured a positive calcium and phosphorus balance in two patients with renal rickets whom they treated with large doses of alkalies and vitamin D. It is possible that purgative alkalies can exert some ill effect both as purgatives and as alkalies.

Deficient sunlight. Weissenbach and Lièvre (1938) ascribed two cases of osteoporosis wholly, and two partly, to this cause.

Senility. The question of age has been discussed sufficiently to indicate that the condition under discussion is not purely one of advanced years, although it embraces the more severe cases of senile osteoporosis.

Achlorhydria. Meulengracht (1938) observed this in eight cases out of 19. Black, Ghormley, and Camp (1941) found achlorhydria in 11 of 29 investigated cases of senile osteoporosis of the spine. Four out of 12 of our patients who were investigated had achlorhydria; a fifth had pernicious anaemia and almost certainly complete achlorhydria. It is doubtful whether this alone without dietary deficiency would suffice to produce the bony changes. Nevertheless, these should be looked for in cases of known or suspected achlorhydria.

Syphilis. One of our earliest cases of osteoporosis of the spine was in a man of 32 years suffering from syphilis. This case did not resemble syphilitic generalized osteitis, and, except in the matter of age, was both clinically and radiologically similar to the cases here described. The Wassermann reaction was positive in this case, though negative in the other 15 cases of spinal osteoporosis which were tested. He had received a great deal of treatment (reputedly 48·1 gm. of arsenic and 30·1 gm. of bismuth in $5\frac{1}{2}$ years), and we were inclined to think that this, rather than syphilis directly, might have played a part in the decalcification; his dietetic habits were unknown. Calcium and phosphorus balance investigations in his case are given later. Racouchot (1939) described a case of painful osteoporosis of the spine in a syphilitic woman aged 36 years who had been treated with novarsenobenzol, cyanide of mercury, iodized oil, and hydroxide of bismuth. Of the last she had received 37·5 gm. (equivalent to 30·1 gm. of metallic bismuth) in $2\frac{1}{2}$ years, and a bismuth line was present on the gums. Whenever the drug was given the pain became worse. The author ascribed the spinal osteoporosis to the bismuth intoxication. Aggravation of symptoms followed the administration of mercury, bismuth, and iodine in an established case of osteoporosis having a negative Wassermann reaction (Caussade and Tardieu, 1932). The typical condition has occurred in a tabetic patient of 64 years who was thought not to have received anti-syphilitic treatment (Thomas, Shaeffer, and Huc, 1933). One of the figures (No. 9) illustrating an osteoporotic spine in the paper of Lance, Girard, and Lance (1938) shows, without comment, tracts of gluteal injections of a radio-opaque material. One of Meulengracht's patients was syphilitic, but his diet had been very deficient. (Meulengracht and Rothe Meyer, 1937; Meulengracht, 1939.)

Other conditions which might interfere with absorption. Meulengracht (1938) reported a case complicating pyloric stenosis; Ravault, Graber-Duvernay,

and Léger (1939) described a case complicating gastro-enterostomy, but diet was probably the major factor here. Meulengracht drew attention to similar changes in non-tropical sprue, which is probably an example of idiopathic steatorrhoea (Gee's or coeliac disease); in this disease various manifestations of rickets and osteomalacia are familiar, and they may include spinal changes (Bennet, Hunter, and Vaughan, 1932; Miyakawa and Stearns, 1942). Holmes (1939) reported an example of generalized osteoporosis with the typical spinal changes and without pelvic deformity in a case of chronic diarrhoea of unknown origin, possibly tropical sprue; steatorrhoea was not demonstrated. Delahaye (1938) mentioned a case of dorsal kyphosis with marked osteoporosis in a patient with chronic amoebic enteritis.

Hypopituitarism is sometimes associated with generalized osteoporosis. Moffat (1933) described osteoporosis of the spine, with the changes described above, in a boy of 19 years considered to be suffering from hypopituitarism.

Hyperthyroidism is often accompanied by osteoporosis, with excessive calcium excretion. The loss can rarely be so severe as to give the changes described here, but Hunter (1935) has reported one case, though the published radiograph does not show advanced changes. One of the patients with osteoporosis described by Ravault, Graber-Duvernay, and Léger (1939) had suffered from Graves' disease 25 years before the onset of spinal symptoms; two others were complicated by non-toxic goitre. One of our patients had been treated for Graves' disease for a period of eight months, six years before the onset of spinal symptoms.

Dental condition. Sixteen of our patients had lost all their teeth; of the remaining four patients, one was edentulous in the upper jaw only, one possessed 10 teeth, the third possessed one tooth, and the fourth possessed 12, all requiring extraction on account of periodontal disease. In view of the age of our patients the condition of their teeth cannot be considered as exceptional.

Scurvy. Deficiency diseases tend to occur together in the same patient. One of Meulengracht's (1938) patients had scurvy. One of our patients gave a history suggestive of scurvy 15 years previously. When she was seen the excretion tests showed that she was grossly unsaturated with ascorbic acid. Three other patients who were tested showed respectively gross, moderate, and slight degrees of unsaturation.

Fractures, other that those of vertebrae. One of our patients had sustained a Colles fracture 10 months before, and another had had an intracapsular fracture of the neck of the femur, 10 months before. In each case the fracture resulted from material injury, a fall from a step-ladder, and in each case bony union occurred satisfactorily. Another patient had suffered from broken ribs four times in the preceding five years, twice spontaneously. Yet another sustained a fractured inner malleolus from slipping while in hospital for investigation of her osteoporosis. Other cases have been reported (Meulengracht, 1939; Lance, Girard, and Lance, 1938; Ravault, Graber-Duvernay, and Léger, 1939).

Heterotopic calcification. The radiographs of one of our patients showed dense calcification of the costal cartilages, which is commonplace, and of the rings of the trachea and bronchi, which is infrequent. Concomitant calcification of the aorta has been described by other observers.

Results of Pathological Investigations

The serum-calcium was estimated in 17 of our 20 cases. Seven gave figures between 8 and 9 mg. per 100 c.c.; seven between 9 and 10 mg.; and three between 10 and 11 mg. The accepted normal range is 9 to 11 mg. per 100 c.c. of serum. Ravault, Graber-Duvernay, and Léger (1939) similarly found the serum-calcium slightly diminished in the five patients investigated. Lance, Girard, and Lance (1938), on the other hand, found the blood-calcium normal or sometimes raised. Similarly Meulengracht (1939), among his 19 cases of osteoporosis, found mostly normal values in the 12 cases investigated. In 92 determinations in 68 cases of senile osteoporosis of the spine Black, Ghormley, and Camp (1941) found figures between 7·8 and 12·7 mg. of calcium per 100 c.c. of serum; the 'great majority' of readings were between 9 and 11 mg., and the average value was 9·8 mg.

The serum inorganic phosphorus, estimated in the same cases of ours as the serum-calcium, was distributed as follows: below 2 mg. per 100 c.c. one; 2 to 3 mg., five; 3 to 4 mg., nine; 4 to 5 mg., one; 5 to 6 mg., one. All, except the first and last figures, are within the normal range for the adult. The serum-phosphorus was estimated before treatment in nine of Meulengracht's (1939) cases; the values were all between 3 and 5 mg. per 100 c.c. Black, Ghormley, and Camp (1941) reported 77 determinations of the serum inorganic phosphorus in 58 cases, with results varying between 2·1 and 6·5 mg. per 100 c.c., and a mean of 3·4 mg. per 100 c.c. Darley, Gordon, and Matchett's (1942) figures were of the same order. In Meulengracht's series and ours there was little tendency for calcium and phosphorus values to show either a direct or an inverse relationship. The distribution of cases for various serum inorganic phosphorus and serum-calcium levels in Meulengracht's and the present series is shown in Fig. 2.

Calcium and phosphorus balances. We are able to report only two balance experiments, as we considered the conditions in the wards of our Emergency Medical Service hospital unsuitable for accurate work. One experiment was carried out before the war on a man under good conditions, but he was the one syphilitic patient in the series. He was given a weighed diet which contained 1,000 mg. of calcium and 1,353 mg. of phosphorus. In the first period he showed a negative balance of 271 and 253 (average 262) mg. of calcium in spite of the large intake. By a mistake, the phosphorus was not estimated. He was then given 12,000 i.u. of vitamin D and 60,000 i.u. of vitamin A for nine days. This caused a decrease in the output of calcium in the urine from 261 mg. to 192 mg., but the daily balance was still a negative one of −36 to −145 mg. In this experiment the phosphorus

was estimated, and there was a daily negative balance of 320 mg. The dose of vitamin D was increased to 16,000 i.u. and that of vitamin A to 80,000 i.u., and the balance was repeated after an interval of 145 days. The patient then had a positive calcium balance and was retaining 93 mg. (average for

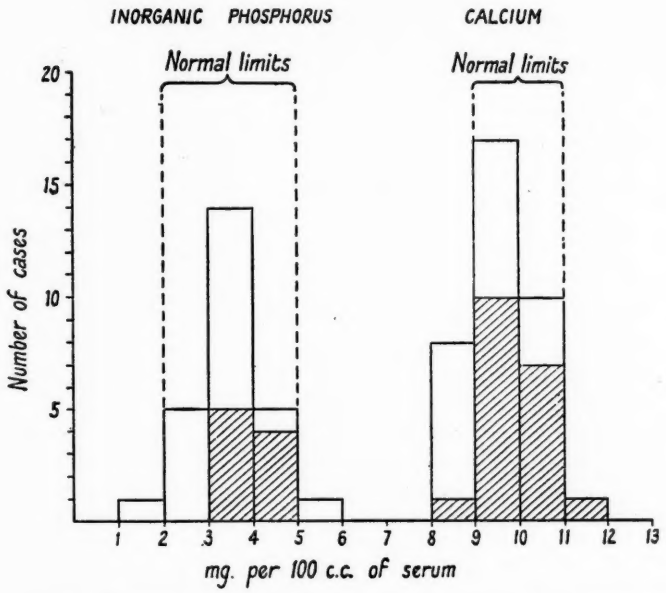

FIG. 2. Diagram to show grouping of patients according to serum inorganic phosphorus and serum-calcium concentrations. (Meulengracht's series cross-hatched; present series, plain.) The values tend to be lower in the present series than in Meulengracht's.

the eight days). He was still losing a little phosphorus, 40 mg. a day, but this was a considerable improvement.

The calcium balance of a second patient was determined by Dr. J. N. Cumings at the National Hospital, Queen Square. This patient had a very advanced degree of osteoporosis. She took a diet without additional vitamin D which contained 1,550 mg. of calcium a day for six days and the average retention of calcium was 750 mg. daily. This result was so surprising that it was checked in every possible way and no error of collection was discovered. It was repeated six weeks later and the positive balance was 650 mg. It must be concluded that this patient, whose vertebrae were mere 'ghosts', was able to store calcium easily when a high calcium diet was given.

Most reports have shown that the patients were losing calcium and phosphorus.

The blood-phosphatase was estimated in the same 17 cases as the calcium and phosphorus. It was normal or just above normal in all except four. In one, a raised figure was explained by advanced renal disease; in the other

three, recent collapse of a vertebral body was suspected, and bone repair would account for the high figures. These observations agree with those of other observers.

Dark adaptation. Vitamin D deficiency may be expected to be accompanied often by the deficiency of vitamin A. The dark adaptation of four of our patients was investigated by Mr. E. W. Godding, of the Crookes Laboratories, and found to be materially deficient. Meulengracht (1938) made a similar observation in one case.

The erythrocyte sedimentation rate was somewhat raised in four of our cases, but there was independent reason in all (pernicious anaemia, gout, and two cases of hyperpiesia); in the other seven in which it was performed it was normal. Unexplained high figures appeared in two out of Meulengracht's (1938) four cases; it was not repeated, so that the elevation may have been from transient causes. Similarly, Black, Ghormley, and Camp (1941) had some unexplained high readings, but they recorded no repeated investigations.

The blood counts and haemoglobin estimations gave normal results in all our patients, except the one with pernicious anaemia and the one with aplastic anaemia. Other observers have found the blood count normal unless the condition was complicated by another cause for the anaemia.

Renal function tests. The blood-urea, estimated in 16 of our patients, was found to be materially high (58 and 60 mg. per 100 c.c.) in one of the two patients who might have had mild Cushing's syndrome; renal deficiency was confirmed by the urea clearance test, and the patient later died in uraemic coma. The serum-cholesterol was estimated in both the cases of suspected Cushing's syndrome, and found to be raised in both (free, 82 mg. + ester, 218 mg. = total, 300 mg. per 100 c.c.; and 81 + 264 = 345; normal, 100 to 230 mg. per 100 c.c.).

The faecal fat was estimated in three cases in which there seemed a possibility of mild old-standing steatorrhoea, but the findings were normal.

Necropsy Findings

Three of our patients have died, one from broncho-pneumonia complicating aplastic anaemia, a second from cerebral haemorrhage, and a third from uraemia. In the first two instances post-mortem examinations were made, but unfortunately without our knowledge. The endocrine system was not critically examined, and no specimens were preserved.

In the first case a thick sliver (Plate 8, Fig. 6*a*) was easily removed from the vertebral column with a knife. The vertebral bodies were biconcave and more squat than usual, the intervertebral disks were enlarged and biconvex. The degree of osteoporosis was so extreme that the vertebrae resembled the red marrow of a long bone and were fleshy in consistency. In the second case the spine from the fifth thoracic to the second lumbar vertebrae was bisected sagitally (Plate 8, Fig. 7). The osteoporosis was much less marked and most of the vertebrae still showed a bony texture. The nuclei pulposi

bulged from the cut surface, so that some of their turgor still remained in spite of the expansion of the disks. The cartilaginous plates seemed much thinner than usual.

Professor G. Hadfield cut sections from the second and third lumbar vertebrae and the intervening disk of the first specimen, and from the eleventh and twelfth vertebrae and intervening disk of the second specimen, and compared them with the sections of the spine of a man of approximately the same age. He reported as follow:

Case 1. Under low power the following changes are seen:

Considerable and irregular reduction in thickness of the bony corticalis enclosing the spongiosa of the vertebral bodies, this change being most severe in that part of the corticalis in contact with the thinned-out cartilaginous plates above and below each disk (Plate 8, Fig. 8 and Plate 9, Fig. 9).

A striking reduction in the amount of cancellous bone of the spongiosa of the vertebral bodies. The normal pattern of anastomosing bony columns is reduced to a few scattered and isolated spicules of bone which are coarsely and irregularly fibrillated, the osteocytes being large, swollen, and degenerated. There is no suggestion of fibrous substitution or presence of uncalcified osteoid or osteoclastic resorption (Plate 9, Fig. 10).

In addition to the reduction in thickness of the cartilaginous plates seen with the naked eye, low power examination shows many breaches of continuity in the cartilage through which the disk substance comes into direct contact with the spongiosa of the vertebral bodies (Plate 9, Fig. 11). The cartilage cells are reduced in number, very greatly reduced in size, and closely packed together. They have obviously been subjected to considerable pressure and the appearances are those of simple pressure atrophy.

The disks themselves show no clear division into annulus and nucleus pulposus, although the latter structure can be indistinctly identified microscopically from its loose structure. The disks look abnormally compact and stain more deeply than normal. Along the whole length of the cartilaginous plates there is irregular invasion of the annulus by swollen and apparently immature cartilage cells suggesting irregular cartilaginous metaplasia. Here and there these cells lie in a lightly calcified matrix. The cells of the disk stain weakly and the fibre system is irregular and erratic.

The sequence of events as judged from these sections appears to have been:

1. Simple atrophy of the bony framework of the vertebral bodies not due to fibrous substitution or osteoclastic resorption.
2. Expansion of the annular portion of the intervertebral disks with prolapse into the vertebral bodies.
3. Pressure atrophy and loss of continuity of the cartilaginous plates.

Case 2. The disk shows considerable expansion into the spongiosa of the body. The expansion is much more regular than in the first case. The cartilaginous plate on either side of the disk is well defined and the margin in contact with the disk substance shows relatively little irregularity. There is obvious atrophy of the bony framework of the vertebral body, but this is quantitatively much less serious than in the first case. Uncalcified osteoid tissue is absent.

The nucleus pulposus is easily recognizable, but its fibre system is irregular and its cells are scanty. Under higher powers the cartilaginous plates on

either side of the disk show close packing of cartilage cells with reduction in cell size.

The changes found strongly suggest that the pathological process in this case is the same as that found in the first case, but at a much earlier stage.

The most conspicuous microscopic changes were the extreme osteoporosis of the vertebral bodies, without osteoid tissue formation, and the attenuation of the cartilage plate separating the rest of each disk from each body.

Distinction from the osteomalacias. The two clinical forms of osteomalacia, puerperal (or pregnancy) and hunger osteomalacia must be distinguished from the osteoporosis which we have described. The gross changes in the vertebral column are similar in all three types.

Puerperal osteomalacia is conspicuously associated with pregnancy and lactation in women living on grossly deficient diets and, in some cases, without adequate sunlight. It has a fairly rapid onset, and is associated with a low concentration of blood-calcium and often with tetany. Its effects fall on the pelvis and spinal column, but the limbs also may be affected. Spasm of the adductor muscles of the thighs, a waddling gait, and bony tenderness are prominent features.

Hunger osteomalacia or famine osteopathy (Cramer and Schiff, 1920; Dalyell and Chick, 1921; Hume and Nirenstein, 1921) such as that found in Vienna after the war of 1914–18, affected some of the very poor of either sex from adolescence (when the disease merged with late rickets) upwards; the commonest ages were between 40 and 70 years, and especially between 60 and 70 years. The clinical features resembled those of puerperal osteomalacia in the painful movement, waddling gait, bony tenderness, and spasm of adductor muscles, with frequently low blood-calcium concentration, Chvostek's sign, and sometimes frank tetany. The osteoporosis, though most pronounced in the trunk, was generalized, and spontaneous fractures of the long bones might occur, but the pelvis was little if at all deformed, a striking distinction from one of the most characteristic changes of puerperal osteomalacia. The symptoms of hunger osteomalacia were less marked in the summer, as occurred also in one of our patients who had backache during four successive winters. Although the epidemics of hunger osteomalacia were associated with an even greater increase in cases of infantile and late rickets, there is said to have been no proportionate rise in the incidence of puerperal osteomalacia. If the acute symptoms due to sudden vertebral collapse be excluded, the three conditions can be arranged in this descending order of severity and rate of onset of symptoms: puerperal osteomalacia, hunger osteomalacia, and the osteoporosis under discussion.

Clinically puerperal osteomalacia and hunger osteomalacia show some striking differences from osteoporosis, since none of our patients had pain on walking, a waddling gait, spasm of the adductor muscles, or bony tenderness. In the osteomalacias, the condition has a fairly rapid onset, whereas in osteoporosis the onset is certainly gradual until a vertebra collapses. The pathology is also quite different. In osteomalacia an excess of osteoid tissue

(Pommer, 1885; Maxwell and Turnbull, 1930; Maxwell, 1935) is formed instead of bone, so that the layer of bone is thinner than usual and there is a broad seam of osteoid tissue which outlines the trabeculae of the bone. The sections from our two fatal cases show that the bone is thinner than usual and that the seam of osteoid tissue is of normal thickness. Thus both the clinical and pathological evidence makes it clear that the condition here described is different from osteomalacia.

Discussion of the Aetiology

The cause of the osteoporosis can now be considered in the light of this evidence. It must result from the failure of ossification to keep pace with bone resorption. This failure may result either from increased destruction or from dimished construction. No histological evidence was found of the former. The latter is the more likely explanation and the following factors must be considered.

Lack of sufficient vitamin D in the diet. The evidence which we have brought forward shows that the osteoporosis differs in many respects from osteomalacia. The latter is believed to be due to lack of vitamin D, and recovery takes place rapidly when adequate amounts of the vitamin are given. It does not seem conceivable that osteoporosis with its different pathology can be due to this cause.

The association of some cases with other diseases such as scurvy due to lack of vitamin C, and with poor dark adaptation, due to lack of vitamin A, may be no more than an accidental association though it may be of importance. Ascorbic acid plays an active part in the repair of bone as Bourne (1942 *a*, *b*) has shown. One of our patients almost certainly had scurvy 15 years previously and was grossly unsaturated; one other patient was also grossly unsaturated, one moderately so, and the other only slightly; but unsaturation is frequent, in wartime at all events. The other 16 patients showed no obvious sign of scurvy, but were not tested. It is conceivable that patients may just take enough vitamin C to prevent any obvious signs of scurvy, but that the amount taken may be insufficient to allow of proper repair of the bone. We feel that this point requires further investigation.

It is not believed that lack of vitamin A plays any part in bone repair.

The low calcium and phosphorus content of the diet possibly intensified the dietary restrictions in war time. It seems probable that these factors play some part in causing the condition. The amounts which our patients took are on the low side and this is especially the case with the phosphorus. The second calcium balance which we reported is in favour of this hypothesis. The bodies of the vertebrae were reduced to 'ghosts', but when a diet containing 1,550 mg. of calcium was given no less than an average of 750 mg. were retained each day of the experiment; that is, calcium was retained if enough were given. Unfortunately the phosphorus balance was not determined in this case.

Achlorhydria. This was present in a third of our cases, and it is possible that it plays a part, but the association is not clear.

The effect of chronic diarrhoea, when it is caused by steatorrhoea, may be decisive, since the fatty stool may sweep out before absorption both the calcium and phosphorus, as well as the vitamin D contained in the fat. Diarrhoea due to purgation is more difficult to understand, but may perhaps be a contributory factor.

Endocrine disturbances, such as those due to thyroid excess or pituitary changes, probably play some part in a few cases.

The age incidence is consistent with a disease progressing over a period of years before the onset of acute symptoms. The discrepancy between the age of onset of these in the two sexes confirms the general impression that many factors may contribute to the osteoporosis.

Differential Diagnosis

Seeing that 20 cases were met in less than five years in the course of ordinary hospital practice, we cannot think them rare, and there must be many which pass unrecognized. A clinician should have no difficulty in diagnosing these cases provided that he is familiar with their characteristic clinical and radiological picture. It is important to recognize that the poor quality of the films depends on the general lack of calcium in the vertebrae and not on the poor technique of the radiographer. If this is remembered the diagnosis may be made considerably earlier and before gross deformity has occurred. If all patients who complain of persistent pain in the back were properly investigated, the diagnosis should be made much earlier. A few conditions which may mislead are worthy of review.

Fibrositis and arthritis. Cases of osteoporosis are often erroneously diagnosed as one of these conditions, usually through want of radiological examination. With a diagnosis of arthritis, one of our patients had received 'X-ray baths'. These were followed by symptoms of a severe anaemia, which caused carcinoma of the stomach to be suspected and a laparotomy to be performed. A correct diagnosis of osteoporosis and aplastic anaemia was made before death. Almost certainly the osteoporosis preceded the treatment.

Malignant new growths. Probably the commonest radiological mistake is to diagnose malignant disease when osteoporosis of the spine is present, a serious matter because of the difference in treatment and prognosis. The tendency for some vertebrae to be more affected than their neighbours in cases of osteoporosis, as in malignant disease, should be remembered. Secondary carcinoma, in the absence of an obvious primary growth or demonstrable bony metastasis elsewhere, usually destroys a vertebral body without obvious change in its neighbours. Black, Ghormley, and Camp (1941) attach much importance to two pathological tests, the erythrocyte sedimentation rate and the blood films; a rapid sedimentation and immaturity of myeloid cells suggest that the bony changes are due to carcino-

matosis. The diagnosis of malignant disease had been made in one of our cases.

Diseases involving the bone-marrow. Myelomatosis and the leukaemic type of myelomatosis, plasma cell leukaemia (Hochwalt, 1932), may give the changes characteristic of spinal osteoporosis, so that Bence-Jones proteinuria should always be sought. Bone changes of one kind or another occur in both lymphocytic and myelocytic leukaemias, especially in the aleukaemic (subleukaemic or leucopenic) forms. Craver and Copeland (1935) reported an incidence of six among 68 cases of lymphocytic leukaemia, and one in 82 cases of myelocytic leukaemia. Baty and Vogt (1935) found bone changes in 30 out of 43 leukaemic children X-rayed. The outstanding change has been osteoporosis, and the last-named authors reproduced a spinal radiograph having much in common with the condition here described. Bouchut, Levrat, and Guichard (1934*a*, *b*) summarized some fatal cases of spinal osteoporosis associated with myeloid dysplasia; they considered these cases to be examples of aleukaemic myelocytic leukaemia (aleukaemic myelosis), and named the condition *la myélose osteomalacique*. One of our patients, a woman aged 67 years, whose vertebral radiographs showed the same characteristics as those of our other patients, was found to be suffering from chronic lymphocytic leukaemia, and she has been excluded from our series. The spinal deposits in such conditions as Hodgkin's disease and Gaucher's disease are also a source of difficulty. Good illustrations of Gaucher's disease and of myelomatosis radiologically mimicking osteoporosis of the spine are given respectively by Schein and Arkin (1942) and Moffat (1933). In Gaucher's disease, myelomatosis, and the leukaemias, specially the aleukaemic forms, sternal marrow biopsy may settle the diagnosis. Paliard, Guichard, Muller, and Viallier (1938) suggested its use in distinguishing cases of aleukaemic leukaemia with spinal osteoporosis from those of senile osteoporosis, in which they found the marrow normal.

Ankylosing spondylitis and advanced osteoporosis of the spine alike present pain, rounded kyphosis, stiffness of the dorsal and lumbar spine, and restriction of chest expansion. Ankylosing spondylitis however affects men more often than women, it usually becomes manifest between the ages of 20 and 30 years, it always shows radiological evidence of sacro-iliac arthritis or ankylosis, and is almost invariably associated with a substantially raised erythrocyte sedimentation rate.

Spondylolisthesis gives the shortening of the lumbar region and oblique dorso-lumbar folds seen in advanced cases of osteoporosis, but the radiograph has an entirely different appearance. One of our cases of osteoporosis was complicated by spondylolisthesis at the usual level ($L_5 - S_1$). This condition results from a breach of bony continuity in each side of the neural arch of the fifth lumbar vertebra. The breach is considered to be of developmental origin in most cases. In cases of osteoporosis it might just conceivably be of dietetic origin and comparable with the Looser's zones or bands of rarefaction which result from certain dietary deficiencies; this hypothesis seems unlikely.

Tuberculosis of the spine should always be considered in a case of stiff painful back, especially if associated with kyphosis. The diagnosis is settled by the radiological appearances which are characteristic. In tuberculosis two vertebral bodies and the intervening disk are affected early and an abscess develops; the erythrocyte sedimentation rate is usually increased. Tuberculosis of the spine had been diagnosed in one of our cases.

Paget's disease sometimes manifests itself in the spine alone. In such instances the texture of the affected vertebral body or bodies is coarser than in osteoporosis, and collapse is associated with lateral expansion of the vertebral body without much concavity of its upper and lower surfaces. The blood phosphatase is usually more than doubled in Paget's disease, if it is of considerable extent and activity.

Angioma of a vertebra gives in the radiograph a 'honeycomb' appearance which may sometimes be confused with that of osteoporosis. In the angiomatous condition, however, the texture is much coarser, usually only one vertebra is affected, and collapse is unusual.

Fracture of a vertebral body and Kümmell's disease. Collapse of one of the osteoporotic vertebrae, really a pathological fracture, may be mistaken for an ordinary fracture, or for Kümmell's (or Verneuil's) disease (Lance, 1930). This name should be reserved for post-traumatic collapse of a vertebral body without previous demonstrable fracture. These conditions may be distinguished by the history and by the radiological appearance of the other vertebrae. Moffat (1934) pointed out that an adjacent intervertebral disk is usually diminished in traumatic fracture, whereas the disks are enlarged and biconvex in osteoporosis.

Hyperparathyroidism causes widespread bone changes of a fairly distinctive character. The diagnosis is confirmed by the high blood-calcium and low blood-phosphorus.

Senile kyphosis. Although this term is logically applicable to any form of kyphosis of the elderly, such as the condition under consideration, osteitis deformans, and various kinds of arthritis, the term is ordinarily applied to kyphosis resulting from degenerative changes in the intervertebral disks, which become narrowed and often calcified anteriorly.

Osteogenesis imperfecta sometimes shows increased biconcavity and occasional wedging of vertebral bodies, as part of a general osteoporosis (Bohne, 1928; Kersley, 1935).

Cushing's (1933) syndrome. Spinal changes, indistinguishable clinically and radiologically from those described here, are sometimes found in Cushing's syndrome with osteoporosis. Broster (1943) suspects that this is confined to the true cases of pituitary basophilism as distinct from the adreno-cortical syndrome. It has been suggested that cases of osteoporosis associated with obesity and hypertension may constitute a *forme fruste* of Cushing's syndrome; two such cases are included in our series, but the diets were very deficient in calcium and phosphorus. A frank case of Cushing's disease with spinal osteoporosis has been excluded.

Treatment

The treatment we have adopted falls under two heads, general or medical and local or orthopaedic.

Medical treatment. This has varied considerably while we have been observing these patients. The diet and habits have always been regulated, but varying amounts of calcium, phosphorus, and vitamin D have been given. The calcium has been given in various forms, calcium carbonate, calcium lactate, calcium gluconate, and sodium calcium lactate. In the later cases phosphorus has been given combined with calcium or calcium phosphate. The calcium and phosphorus content of the various salts is set out in Tables IV and V. We have found that calcium phosphate in a dose of 1 gm. (15 gr.) three times a day is well tolerated; it supplies 1 gm. of calcium and 0·6 gm. of phosphorus daily. If it is thought desirable to give a higher ratio of phosphorus to calcium, a mixture of three parts of calcium phosphate with one part of sodium phosphate exsiccata might give better results; 4 gm. (a level teaspoonful) twice a day would then supply 2 gm. of calcium and 1·6 gm. of phosphorus. The powder is easy to take, but we have not so far tried it on any patients.

TABLE IV

The approximate calcium content of various salts

Salt	Calcium percentage	Calcium supplied by 3 gm. of salt	Approximate dose of salt required t.d.s. to supply 1 gm. of calcium daily
Calcium carbonate	40	1·2 gm.	1 gm. (gr. 15)
,, phosphate (at 85%)	33	1·0 gm.	1 gm. (gr. 15)
,, lactate	13	0·52 gm.	2 gm. (gr. 30)
,, gluconate	9	0·27 gm.	4 gm. (gr. 60)
,, sodium lactate	8	0·24 gm.	4 gm. (gr. 60)

TABLE V

The approximate phosphorus content of various salts

Salt	Phosphorus percentage	Phosphorus supplied by 3 gm. of salt	Approximate dose of salt required t.d.s. to supply 1 gm. of phosphorus daily
Acid sodium phosphate (Sodium dihydrogen phosphate)	20	0·6 gm.	2 gm. (gr. 30)
Calcium phosphate	20+	0·6 gm.+	2 gm. (gr. 30)
Sodium phosphate 'exsiccata' (Disodium hydrogen phosphate)	21	0·6 gm.	2 gm. (gr. 30)

It is of interest to consider the quantity of supplementary calcium which must be absorbed in the food and as a medicine in order to stop the progress of decalcification, and, further, to restore the bones to their normal density. Leitch (1936) calculated that the loss of calcium by one of Meulengracht and Rothe Mayer's (1937) patients was of the order of 91 mg. daily over a period of 10 years. To prevent progress of the disease it would be necessary for this amount of supplementary calcium to be absorbed. If double this

supplement were absorbed, that is, 182 mg. daily, there would also be slow recalcification which would be complete at the end of 10 years. To achieve the same result in one year, it would be necessary for the patient to absorb a daily calcium supplement of 1,820 mg. This amount is very large and a retention of 300 to 400 mg. seems as much as can be expected. At least five to six years must elapse before the skeleton could regain its former calcium content. This calculation may explain why the skiagrams of our patients taken one to three years after the diagnosis was made still showed no evidence of any increase in density.

Vitamin D has a specific effect in curing rickets and osteomalacia, and we have given it in doses varying from 3,000 to 30,000 i.u. daily without observing any striking changes in the radiographs of our patients. We have not seen any of the ill effects reported by Tumulty and Howard (1942). They gave 750,000 i.u. for 10 and 17 days respectively to two young men in the hope of causing fractures to unite more quickly. The patients developed nausea and vomiting with signs of mild nephritis, and the serum-calcium rose to 15 and 18 mg. per 100 c.c. We feel that a dose of 30,000 units a day is quite safe, but we now doubt the advantage of these big doses because the pathology of osteoporosis is so different from that of osteomalacia. The question therefore arises whether it is worth while giving any vitamin D. We think that it should be given because it is said to aid the absorption of calcium and phosphorus. It is said to be most effective when the contents of the small intestine are acid. We therefore think in the present state of our knowledge that the large doses of 30,000 i.u. probably had no specific value, but that small doses of 5,000 to 10,000 i.u. may aid in the absorption of calcium and phosphorus and can do no harm.

If the osteoporosis is associated with steatorrhoea the fat intake should be as small as possible. Full doses of calcium phosphate and vitamin D, say 10,000 i.u. should be given, and treatment with ultra-violet light may be of assistance.

Orthopaedic treatment. Almost every patient was provided with a plaster bed for night use. To this he was accustomed in hospital, because patients need help in acquiring tolerance and eventual addiction. For day use, a steel and leather spinal support was fitted in most cases; in the least severe, mechanical support was dispensed with, and the patient was provided with merely a corset incorporating a light posterior frame to bridge the lumbar spine.

Results of treatment. The clinical condition of our patients was greatly improved and the pain was relieved in nearly all. We thought that this was due to the orthopaedic treatment, and doubted at one time because of the lack of change in the radiographs whether the medical treatment had been of any real value. However, other workers have reported that improvement occurred when medical treatment alone was employed. We now realize that the time necessary for any obvious changes in the radiographs is much greater than we had expected, and we therefore believe that medical

treatment with calcium phosphate and moderate doses of vitamin D should always be used in addition to orthopaedic treatment. This question will be settled when a sufficient period of time has elapsed for observation.

Summary

1. A series of 20 patients with spinal osteoporosis of unknown origin has been observed between 1939 and 1943.

2. The osteoporosis is most marked in the lower part of the back where secondary deformity of the vertebrae occurs. Patients who did not show deformity of the spine are not included in our series. Pelvic deformity such as occurs in puerperal osteomalacia was absent.

3. The symptoms, signs, and radiological appearances are characteristic.

4. The clinical and pathological changes are different from those of osteomalacia.

5. The possible causes of the condition are discussed, but no one factor can be incriminated.

6. The symptoms can be relieved by treatment, but an increase in the calcification of the affected vertebrae was not demonstrated radiographically.

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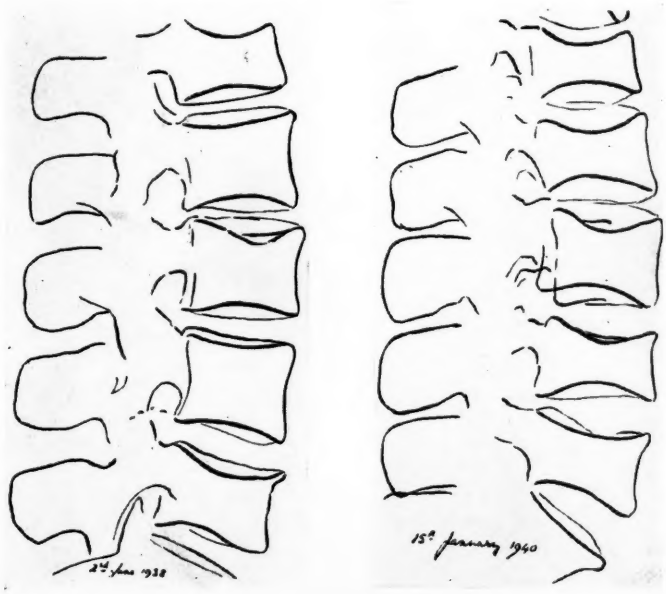
FIG. 3. Lowest thoracic and upper four lumbar vertebrae, showing bi-concavity of the osteoporotic vertebral bodies and 'kissing' spinous processes.

FIG. 4. Lumbar spine, showing bi-concavity of the vertebral bodies, which are osteoporotic, but show greater density where they adjoin the intervertebral disks.



A B

FIG. 5. Tracings from radiographs of the lumbar spine of a case of osteoporosis examined at an interval of 17 months. Telescoping, from softening of each vertebra as a whole, is revealed by the much smaller intervals between the spinous processes in the second tracing (B) than in the first (A).

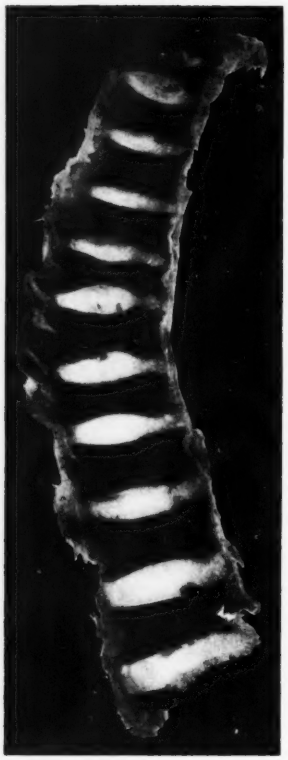


FIG. 6. Specimen removed *post mortem* from the thoracic spine in a case of osteoporosis and aplastic anaemia.

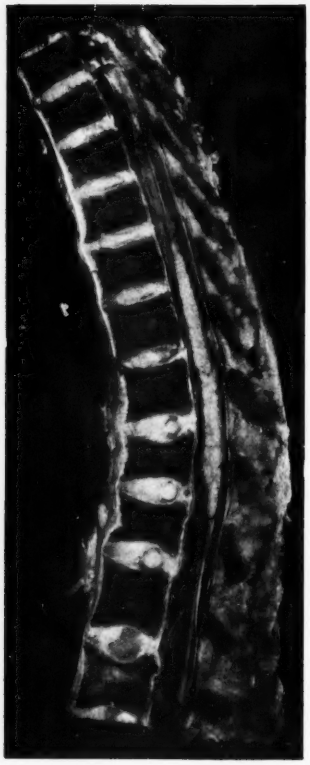
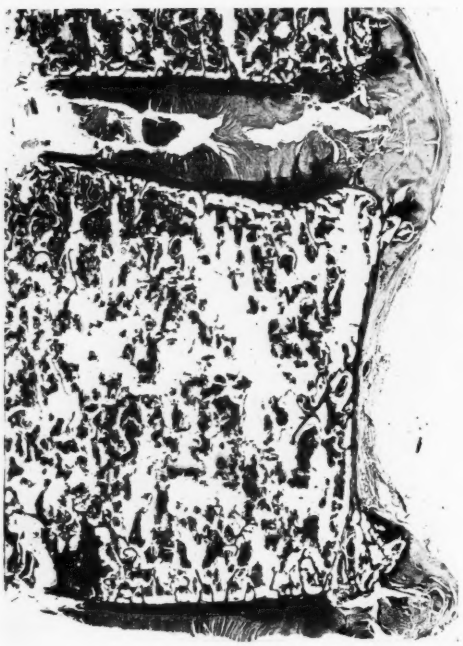
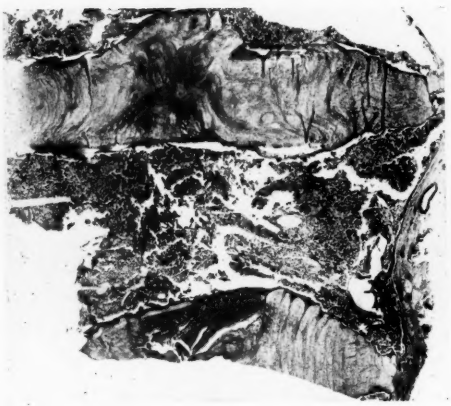


FIG. 7. Specimen removed *post mortem* from the thoraco-lumbar spine in another case of osteoporosis.

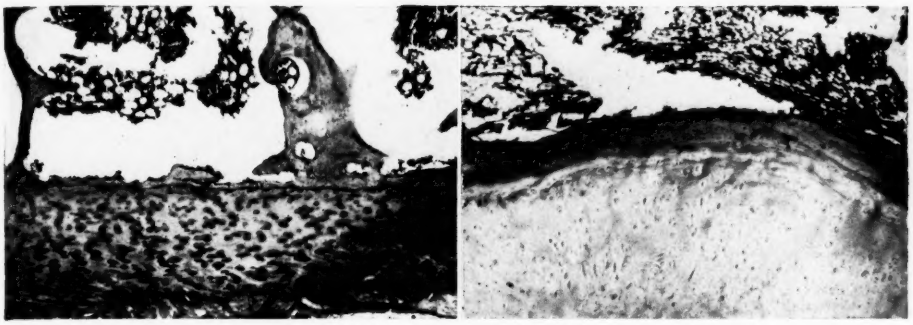


A



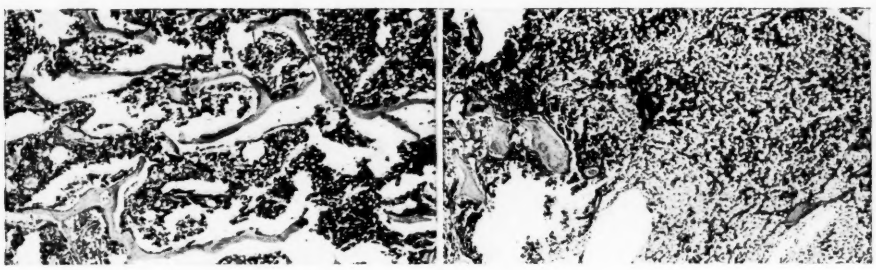
B

FIG. 8. Stained sections from (A) normal senile spine, (B) the first case examined *post mortem*. The swollen, convex disks and concave vertebral bodies characteristic of osteoporosis are shown in (B). (×2·8, but section greatly shrunken.)



A B

FIG. 9. Junction of vertebral body (above) and intervertebral disk (below). (A) normal senile spine, (B) the spine from the first post-mortem examination. In the former, the cartilage plate separating the rest of the intervertebral disk from the vertebral body is well developed and is in contact with the very thin cortex of the end of the vertebral body. In the pathological spine, the cartilage plate is diminished and the adjacent cortex absent. An intermediate condition was seen in the specimen from the other post-mortem case. (×26)



A B

FIG. 10. Texture of cancellous bone of vertebral body from (A) normal senile spine, and (B) the first case examined *post mortem*. Trabeculae are very scanty in the latter. (×13)

FIG. 11. Breach in cartilage plate, allowing herniation of disk substance into the vertebral body, the early stage of a 'Schmorl's node,' from the first post-mortem examination. Radiographic evidence of this change is rarely seen in osteoporosis. (×11)

616.12–008.331.1 : 616.61

RENAL FUNCTION AND PROGNOSIS IN BENIGN HYPERTENSION[1]

By MURRAY McGEORGE

(From the Department of Medicine, University of Otago, New Zealand)

It is customary to divide essential hypertension into two forms, malignant and benign. The exact separation between these is to a large extent a matter of degree and definition, but it would be generally accepted that the malignant cases include those in which the progressive increase in blood-pressure takes place more rapidly, and renal, ocular, and cardiac complications occur at a comparatively early stage. Signs of renal impairment make their appearance, with low, fixed urinary specific gravity, nitrogen retention in the blood, and moderate or severe impairment in renal concentrating power. Albuminuria is present and may be marked, while blood may also be present in the urine. In the benign form, on the other hand, though death frequently results at a much later stage from failure of the cardiovascular system, patients may live to an advanced age and die of unrelated disorders. Benign hypertension may continue for many years without evidence of appreciable renal failure. Since pathological changes are gradually taking place in the arterioles and glomeruli of the kidney, it is likely that with the passage of time gradual impairment in renal function may occur. In the present paper the observations made on the renal function in hypertension have been confined to cases which, it is felt, would be universally accepted as benign.

Fishberg (1939) stated that in essential hypertension Van Slyke's urea clearance is most often within normal limits; by far the larger proportion of patients can concentrate urine to a specific gravity of about 1025, while the urea concentration test of MacLean and de Wesselow (1918, 1920) gives similar satisfactory results. He noted, however, that in one group of patients, generally older persons in whom there was evidence that hypertension had existed for many years, arteriolosclerotic foci had become so numerous, and had coalesced with one another to so great an extent, that very little functioning parenchyma was left, apparently too little to maintain adequate excretion. He had observed a few cases of this type over a long period, and presumed, from the nature of the anatomical process, that the impairment in renal function which had occurred developed very slowly. It is of interest, therefore, to determine the nature of any defects in renal function which may occur in benign hypertension, and at what stage they make their

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appearance. This information should be of value in assessing the clinical prognosis in a given case. Foà, Woods, Peet, and Foà (1942) found that 15 of 20 hypertensive patients between the ages of 26 and 45 years had urea clearances within normal limits, that is, over 75 per cent. of normal. Freyberg and Peet (1937) studied the renal function of patients between the ages of 21 and 55 years who were about to have bilateral splanchnicectomy performed for hypertension. In the majority, the pre-operative blood-pressure was over 200 mm. of mercury, and in many the urine contained albumin. Of these, 23 out of 46 had a urea clearance above the lower limit of normal, and eight out of 47 were able to concentrate urine to a specific gravity of at least 1029 (Lashmet and Newburgh, 1932, 1933). Corcoran and Page (1940) found that the maximum specific gravity attained was within normal limits (Addis and Shevky, 1922) in only 22 of 72 cases of hypertension, whereas normal values for urea clearance were obtained in 50. Inulin and diodrast clearance tests have recently been developed by Smith and his associates (Smith, 1939; Goldring, Chasis, Ranges, and Smith, 1941), in which it has been shown that in essential hypertension the diodrast clearance is generally decreased, while the inulin clearance remains substantially unaltered.

In hypertension, as in other diseases, Freyberg (1935) found that slight degrees of renal impairment were more likely to be revealed by tests dependent upon the concentrating power of the kidney than by other tests. One of the simplest is the MacLean and de Wesselow urea concentration test. It is of interest, however, to note the limitations placed upon this test by the authors in their original communications (1918, 1920). They state that if after receiving 15 gm. of urea by mouth the patient excretes urine containing 2 per cent. or more of urea 'it is safe to assume that the kidneys are at least fairly efficient'. This test was introduced after the war of 1914–18 and was admirably adapted to its original purpose, the rapid examination of large numbers of soldiers. It was never intended as a sensitive test for the recognition of slight departures from normal, although there has been a tendency to regard it as such, and to assume for it greater sensitivity than its authors originally claimed.

Smirk (1933, 1934) pointed out that greater precision in the recognition of slight grades of renal deficiency resulted if a study were made of the capacity of the kidneys to concentrate urea and sodium chloride simultaneously. The expression $C+U/2$ was suggested as a measure of renal concentrating power, where in a given specimen of urine passed in a four or five hour test after the ingestion of 15 gm. of urea U is the urea percentage and C the chloride percentage expressed as sodium chloride. This particular expression was chosen on the basis of the similarity of the molecular weights of urea and sodium chloride, on account of which the osmotic pressure in the urine due to chloride and urea would be approximately equal to $k(C+U/2)$. The value of $C+U/2$ which was used as the measure of renal function was that derived from the specimen containing the maximum concentration of

urea. This value was found to be greater than 2·0 in practically all normal subjects, provided the diet had not been very poor in chloride, and less than 2·0 in practically all cases of Bright's disease, even in cases where the percentage of urea rose to a normal level. It was found that this test revealed a higher percentage of defects than was shown by the urea concentration test in the early stages of conditions which ultimately cause renal damage, such as infective endocarditis, diabetes mellitus with albuminuria, prostatic obstruction, and hydronephrosis. Since, therefore, the test shows normal function in practically all normal subjects, and also shows a high percentage of deficiencies among patients who are known finally to develop renal defects from various causes, it is fair to assume that the test is one which detects functional impairment at an early stage. Out of six cases with hypertension without congestive failure, Smirk found that in four the renal function was below the normal level, and in only one case was the renal function clearly normal as judged by this test. In the present investigation this work has been continued, and has been extended with special reference to the relationship in non-hypertensive and hypertensive subjects between the renal function and the age of the patient.

Method

Renal function tests were carried out as follows. The subject had nothing to eat or drink after the evening meal of the previous day. At 6 a.m. he emptied the bladder, and had a light breakfast consisting of one egg, one or two slices of bread and butter, and one cup of milk or water. At 9 a.m. 15 gm. of urea were taken dissolved in one cup of water (100 c.c. in the original test). The bladder was emptied at 9 a.m., and then at hourly intervals until 2 p.m. The percentage of urea was estimated by the hypobromite method using 5 c.c. of urine and correcting for temperature, and the percentage of chloride, expressed as sodium chloride, by the method of Volhard (Cole, 1933).

Selection of Subjects

All subjects studied satisfied certain criteria. No patient with a history of nephritis or other kidney disease was included. In every case the urine was free from albumin on personal testing, and in in-patients on routine ward tests as well. There was no oedema or venous congestion, or other evidence of cardiac failure, nor, clinically, of renal disease. The majority were receiving full normal diets, and none had had his chloride intake restricted prior to the test. In several cases in which low urinary chloride concentrations were recorded the plasma-chloride showed little or no reduction below the normal level. Patients receiving dietetic treatment for peptic ulcer were excluded. The accepted blood-pressure was the lowest casual (as distinct from basal) pressure obtained in a series of observations taken personally over a period of a few minutes with the patient at rest. Two groups of subjects were studied.

(1) Those with normal casual blood-pressures, that is, not over 145 systolic, 90 diastolic. These were hospital in-patients or out-patients suffering from conditions such as sciatica, fibrositis, asthma, or osteoarthritis, disabilities which would be unlikely to influence renal function.

(2) Hypertensives, with casual blood-pressures over 170 systolic, 100 diastolic. The majority of these were in-patients, while the remainder were army recruits referred for investigation by medical boards after the discovery of hypertension in routine examinations.

Some of the in-patients had been admitted on account of conditions such as those enumerated in (1) above, and had been found on routine physical examination to have an elevated blood-pressure. Others were known hypertensives, and had been admitted complaining of symptoms such as headache, fatigue, slight dyspnoea, hemiplegia, or transient weak or giddy turns, symptoms which, though common in themselves and occurring not infrequently in patients who are found to have a high blood-pressure, are yet unlikely to have any direct association with kidney disease. The occurrence of these symptoms is not inconsistent with the diagnosis of benign hypertension. Care has been taken to exclude any patient suffering from malignant hypertension, and reference to hospital records covering any re-admissions during periods of a few months up to two years subsequent to the determination of renal function shows that while three patients had died, one from rupture of an aneurysm of the Circle of Willis and two from cerebral thrombosis, no patient was known to have developed progressive renal disease during this period.

Results

Renal function tests were carried out on 62 subjects with normal blood-pressures, whose ages ranged from 16 to 80 years, and on 75 with hypertension, from 24 to 71 years of age. In each case the maximum concentration of urea attained during the course of the test, the concentration of sodium chloride occurring in the specimen of urine containing the maximum concentration of urea (henceforth referred to as 'corresponding chloride'), and the value of C + U/2 calculated from these figures, have been plotted against the age of the subject concerned (Figs. 1 to 6).

Renal function in non-hypertensive and hypertensive subjects, irrespective of age.

Subjects with normal blood-pressures. The 62 subjects with normal blood-pressures were all able to concentrate urea to at least 2·0 per cent. In 57 of these (92 per cent.) the value of C + U/2 was 2·0 or greater, while in the remaining five, all elderly patients, values between 1·6 and 2·0 were recorded. These results correspond closely with those obtained by Smirk, who found that in 30 out of 32 normal subjects the value of C + U/2 was at least 2·0. It therefore appears that for this test the value 2·0 may reasonably be regarded as the dividing point between normal and impaired function. The fact that an occasional patient who on clinical grounds was selected for study as a normal subject was found to have slightly impaired renal function

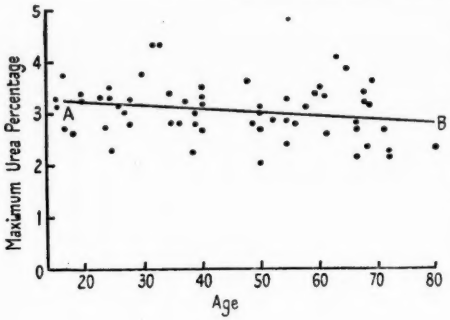

FIG. 1.

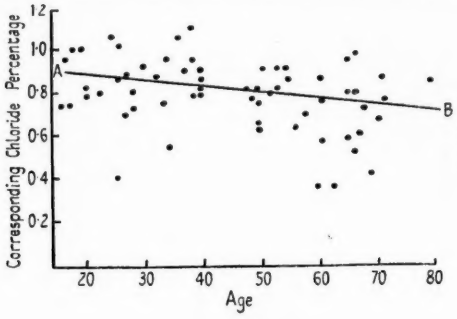

FIG. 2.

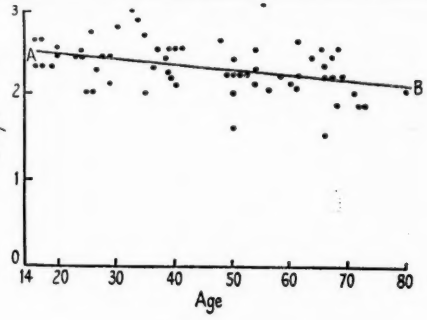

FIG. 3.

FIGS. 1 to 3. Relationship in healthy subjects with normal blood-pressures between age and renal function, as assessed by maximum urea percentage (Fig. 1), corresponding chloride* percentage (Fig. 2), and C+U/2 (Fig. 3).

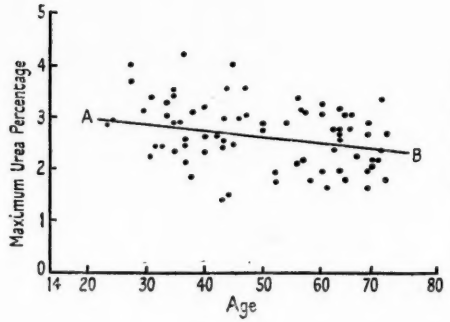

FIG. 4.

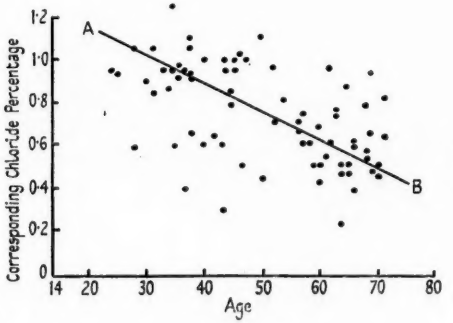

FIG. 5.

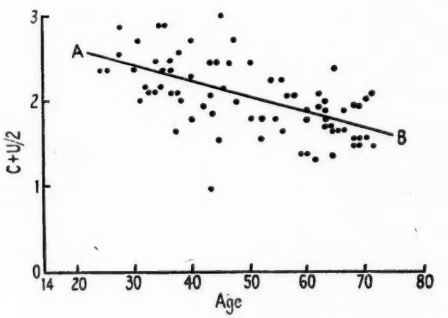

FIG. 6.

FIGS. 4 to 6. Relationship in hypertensive subjects between age and renal function, as assessed by maximum urea percentage (Fig. 4), corresponding chloride* percentage (Fig. 5), and C+U/2 (Fig. 6).

* 'Corresponding chloride' is concentration of chloride occurring in sample of urine containing maximum concentration of urea. Line AB is curve of regression equation.

as judged by this standard, should not invalidate this statement, since it is not unlikely from what follows that slight impairment in renal concentrating power may sometimes occur, especially in older subjects, in the absence of hypertension or albuminuria, or of other clinical evidence of renal disease or degeneration.

Subjects with benign hypertension. In 62 of the 75 cases (83 per cent.) in which the blood-pressure was elevated, a maximum concentration of at least 2·0 per cent. of urea was attained, a result consistent with the generally accepted statement that in the majority of cases of hypertension the urea concentration test indicates satisfactory renal function. In only 41 cases, however (55 per cent.), did the value of C + U/2 reach or exceed 2·0. If the assumption is correct that the value 2·0 does represent the lower limit of normal function in the case of both the urea and the urea + chloride concentration tests, then it would appear that a higher incidence of renal impairment has been demonstrated when renal function was assessed by the ability of the kidneys to concentrate urea and chloride simultaneously than by their ability to concentrate urea alone. In the accompanying table the values of C + U/2 in these cases of benign hypertension have been compared with those obtained in 94 normal subjects (Smirk's and McGeorge's cases) and in 60 cases of chronic nephritis (Smirk). Although in 44 per cent. of cases of benign hypertension the renal function was below the values of C + U/2 obtained in the normal, in the majority the degree of impairment was slight, and no instances of severely impaired function was encountered. In chronic nephritis, on the other hand, the values of C + U/2 recorded were generally far below the normal range, indicating a more serious degree of renal impairment than that occurring in benign hypertension.

Comparison of Renal Function in Subjects with Normal Blood-Pressures, Benign Hypertension, and Chronic Nephritis

	Number of cases		
C + U/2	Normal B.-P.	Benign hypertension	Chronic nephritis
2·0 and over	87	41	1
1·5 to 2·0	7	29	16
1·0 to 1·5	—	5	21
0·5 to 1·0	—	—	22
	94	75	60

The factor of age in relation to renal function in non-hypertensive and hypertensive subjects. The relationship between the age of the subject and the renal function was investigated by a statistical analysis of the data presented in Figs. 1 to 6, the results of which are summarized in tabular form in the Appendix. In the Figures the lines AB are the curves of the regression equations calculated from this analysis, and represent the means of the renal function at varying ages, as measured by the maximum urea and 'corresponding chloride' concentrations, and by the ability of the kidneys to concentrate urea and chloride simultaneously. In the absence of any grounds

for suspecting that, within the age limits studied, regression with age is not uniform, straight lines have been fitted as the simplest hypothesis, while from the graphical data it appears that in each case a straight line does furnish a reasonable approximation to the true curve. In all cases there is a negative correlation between age and renal function, indicating a progressive impairment in function with increasing age. This relationship is illustrated by the curves, which all slope downwards as the older age groups are approached. The slopes, however, are different, but for each of the measures of renal function employed the slope is considerably steeper in hypertension than normal blood-pressure. There is, indeed, no significant difference in function between young hypertensives and young normals, while at the age of 70 years the mean renal function (C + U/2) of hypertensive subjects has fallen off by 31 per cent. of its value at 30 years, as against 10 per cent. for non-hypertensives. Differences of a similar order were also obtained when the maximum urea and the 'corresponding chloride' concentrations were studied separately.

The relationship between renal function and the presence or absence of symptoms frequently associated with hypertension. A distinction was made between cases in which hypertension was apparently symptomless, and those where symptoms were present which might have been associated with this condition. The relative number of patients with symptoms will naturally increase in the older age groups, but there were a few patients over 60 years of age admitted to hospital on account of other disabilities, in whom the presence of symptomless hypertension was discovered on routine examination. Where patients were admitted on account of hypertension with its associated disabilities, the following were the leading symptoms of which they complained, and the frequency of occurrence of these symptoms.

Dyspnoea on exertion	9 cases
Anginal pains	3 ,,
Headache and giddy turns	5 ,,
Transient hypertensive attacks	7 ,,
Hemiplegia (cerebral thrombosis)	8 ,,
Total	32 ,,

In 43 cases there were no symptoms directly associated with hypertension. While it is impossible from the small number of cases to draw any conclusion regarding any individual symptom, it appears from a statistical analysis that there is no significant difference in renal function between the group of cases in which these symptoms considered as a whole were present, and those without symptoms.

Discussion

The term renal function has a somewhat abstract and indefinite meaning, since the kidney is a complex organ performing simultaneously several functions, all of which are of importance to the well-being of the organism.

When the kidney is damaged renal function becomes depressed, and to measure this depression quantitatively tests are applied which estimate the efficiency with which one or other of the specific functions of the kidney is carried out. The three types of function most commonly selected for measurement are (1) the concentrating power of the kidney, (2) its eliminating power (for example, the phenol-sulphonephthalein test), and (3) its ability to clear the plasma of some endogenous or exogenous substance. It is likely that in the early stages of most renal disorders one type of function of the kidney will be depressed before others. Gross damage will be revealed by any test, but minor departures from normal may not be revealed simultaneously by all tests. It is necessary, therefore, to select a test dependent upon a function which is known to undergo early impairment. Comparable results are not even then always obtained from closely related tests of similar type. For example, in hypertension the diodrast clearance is reduced, but the inulin clearance remains materially unaltered (Smith, 1939), while different results again may be obtained for the clearances of urea and creatinine. In investigations of such a condition as essential hypertension, therefore, the incidence of renal impairment as determined by different observers is likely to vary, depending, among other factors, upon the type of test employed, the criteria of normality accepted, and the method adopted in selecting the cases.

In the present investigation a comparison has been made between the renal functions of two groups of subjects, one with normal blood-pressures, and the other with benign hypertension. In other respects these two groups were as nearly comparable as possible, and in particular no patient with albuminuria, venous congestion, or past or present clinical evidence of renal disease was included. It was thus hoped to obtain data concerning the effect upon the renal function of hypertension uncomplicated by other factors.

Renal function was assessed by determining the ability of the kidneys to concentrate urea, and also urea + chloride simultaneously, after ingestion of 15 gm. of urea. In the hypertensive group it was found that 83 per cent. of patients were able to concentrate urea to at least 2·0 per cent., while in only 55 per cent. did the value of $C + U/2$ reach or exceed 2·0. The additional sensitivity of the latter test over the urea concentration test arises from the inclusion of the chloride percentage, which is a more sensitive index of slight degrees of renal impairment than is the maximum urea percentage. Statistical analysis of the data presented in Figs. 1 to 6 shows that the correlation between age and renal function and the decline of function with age based upon $C + U/2$ are both numerically higher than the corresponding values derived from urea concentration tests, while, on the other hand, the coefficient of variation is less for $C + U/2$ than for urea. Tests of probability also show that greater significance may be attached to results calculated from the value of $C + U/2$ than from the concentration of urea.

It was found that in apparently healthy subjects with normal blood-pressures slight impairment in renal concentrating power occurred with

increasing age, the decline in the value of C + U/2 over the 40 year period from 30 to 70 years being 11 per cent. of the mean value at 30 years. A high incidence of renal impairment with increasing age was reported in normal men by Lewis and Alving (1938), who on the basis of urea clearance and blood urea nitrogen tests recorded a decline of 46 per cent. over a 50 year period, that is, 35 per cent. over 40 years. Since, however, no record is published of blood-pressure readings or of the results of urine analysis, it is possible that part at least of this effect may have been due to the presence of hypertension or albuminuria, conditions which occur more frequently among subjects in the older age groups, and themselves may be associated with impaired function.

The mean renal function of young hypertensives was not significantly different from that of young normal subjects, while detailed analysis of the hour to hour changes in the concentrations of urea and chloride after ingestion of urea showed that the response on the part of both groups was essentially similar. It thus appears that young hypertensive subjects show no appreciable impairment of renal function as compared with subjects of the same age group with normal blood-pressures. The average renal function of normal subjects decreased gradually with increasing age, but with hypertensive subjects this regression with age was considerably accelerated. In the 40-year period from 30 to 70 years the rate of decline in concentrating power (C + U/2) was 31 per cent. of the mean value at age 30, that is, approximately three times as great as the decline with normal blood-pressure. A similar relationship also held in the case of the urea and the chloride concentrations considered independently. It seems, therefore, that benign hypertension is not necessarily associated with recognizable renal impairment, especially among patients in the younger age groups, but that impairment may develop later, after hypertension has presumably been present for some considerable period. In all cases of benign hypertension, however, impairment if it occurs is of comparatively mild degree, and consequently in any individual case severe impairment is likely to be an indication of the presence of some complicating factor. A certain number of middle-aged and elderly hypertensive subjects were found to have renal functions within the normal range, but it is probable that in some instances these results would represent a fall below a previous higher level which would have been obtained had the test been carried out when the individual was younger.

Summary

1. A comparison has been made between the renal function of 62 healthy subjects with normal blood-pressures, whose ages ranged from 16 to 80 years, and that of 75 subjects with benign hypertension, from 24 to 71 years of age. In other respects these two groups were as nearly comparable as possible, and in particular no patient with albuminuria, venous congestion, or past or present evidence of renal disease was included.

2. Renal function was assessed by studying the concentrations of urea and chloride in the urine after ingestion of 15 gm. of urea. The capacity of the kidneys to concentrate urea and chloride simultaneously is conveniently expressed by the formula $C+U/2$, where U is the maximum percentage of urea and C the percentage of chloride, expressed as sodium chloride, occurring in the specimen of urine containing the maximum percentage of urea. It has been shown that slight degrees of renal impairment are more readily detected by the use of this expression than by the simple urea concentration test.

3. The average renal function, determined as above, was not significantly different in young subjects, whether hypertensive or not.

4. With increasing age a decline occurred in the renal concentrating power, which was approximately three times as great in the elderly hypertensive group as in the elderly non-hypertensive group.

5. The degree of impairment commonly occurring in benign hypertension is comparatively slight, and no cases with severely impaired function, such as occurs in chronic nephritis, were encountered.

6. Even in elderly subjects with benign hypertension the concentrating capacity of the kidneys may be within normal limits, but in some instances this would probably represent a fall below a higher level which would have been obtained when the individual was younger.

7. There was no significant relationship between impaired concentrating capacity (in the absence of albuminuria) and the presence or absence of symptoms such as headache, dizzy attacks, or cerebral thrombosis, which are frequently associated with benign hypertension.

8. Although the decline in renal function with advancing years can be demonstrated by either the urea or the chloride percentages, there is statistical evidence that the value of the expression $C+U/2$ provides a more accurate index of this decline in both non-hypertensive and hypertensive individuals.

This work was done during the tenure of an Emily Johnston Research Scholarship, University of New Zealand. I am indebted to the Physicians of the Dunedin Hospital for permission to study cases under their care, to Professor F. H. Smirk for valuable advice and assistance, and to Mr. J. W. Williams, Department of Economics, and Dr. H. D. Purves, Goitre Research Department, University of Otago, for help with the statistical analysis.

APPENDIX

Summary of statistical analysis of data presented in Figs. 1 to 6.

TABLE I

Relationship between Age and Renal Function in Subjects with Normal Blood-pressures

	Renal function as estimated by		
	Maximum urea percentage	'Corresponding chloride' percentage	C+U/2
Correlation coefficient between age and renal function	−0·165	−0·37	−0·38
Probability (P)	0·18	<0·001	<0·001
Regression equation (A = age in years)	U = 3·28−0·0049 A gm. per 100 c.c.	C = 0·945−0·0037 A gm. per 100 c.c.	C+U/2 = 2·59 −0·0061 A
Decline between ages 30 and 70 years (percentage of mean at 30 years)	6·7 %	17·7 %	10·4 %

TABLE II

Relationship between Age and Renal Function in Hypertensive Subjects

	Renal function as estimated by		
	Maximum urea percentage	'Corresponding chloride' percentage	C+U/2
Correlation coefficient between age and renal function	−0·25	−0·77	−0·59
Probability (P)	0·021	<0·001	<0·001
Regression equation (A = age in years)	U = 3·17−0·011 A gm. per 100 c.c.	C = 1·413−0·0133 A gm. per 100 c.c.	C+U/2 = 2·97 −0·0184 A
Decline between ages 30 and 70 years (percentage of mean at 30 years)	15·5 %	52·5 %	30·6 %

In these tables the numerical value of P indicates the degree of probability that the correlation coefficient as calculated might have arisen through the chance fluctuations of random sampling. There is thus an 18 per cent. chance that a numerical value as high as or higher than −0·165 might have been obtained as the correlation coefficient between age and maximum urea concentration in non-hypertensive subjects, even although no real correlation actually existed. The correlation coefficients between age and renal function as assessed by 'corresponding chloride' concentration and by C+U/2 are, on the other hand, highly significant, since there is in each case less than one chance in 1,000 that such a result could have arisen by chance.

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A THERAPEUTIC TRIAL OF PENICILLIN IN INFECTIVE CONDITIONS OF THE SKIN[1]

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With Plate 10

Certain skin diseases usually attributed to infection by pyogenic cocci are an important cause of disability in the Army. Such conditions include impetigo and seborrhoeic dermatitis, which are relatively common, and sycosis barbae, ecthyma, and furunculosis, which are rarer. In spite of the known association of *Streptococcus pyogenes* and *Staphylococcus pyogenes* with these conditions, the exact role of bacteria in the aetiology of at least some of them was not clearly defined when chemotherapy with bacteriostatic compounds was first attempted. Favourable therapeutic results were obtained with sulphonamide compounds both in children (Steigman, 1942; Harris, 1943) and adults (Bigger and Hodgson, 1943, 1944; Sheehan and Fergusson, 1943). However, the unfortunate effects of sensitization which may follow the application of sulphonamide compounds to the skin have limited their use, and when penicillin became available for trial in skin diseases it was hoped that it might prove even more effective and that its use would not lead to unpleasant sequelae. Roxburgh, Christie, and Roxburgh (1944) reported that penicillin ointment was effective in the treatment of impetigo and that sycosis barbae, blepharitis, and even eczema which had become secondarily infected, also responded favourably. Taylor and Hughes (1944), using a spray of penicillin solution on the skin, also obtained good results in impetigo and sycosis barbae in soldiers. Both groups of workers noted the resistance of an underlying seborrhoeic state to penicillin, and Taylor and Hughes found that penicillin-resistant strains of staphylococci could often be recovered from the lesions after treatment with penicillin. Treatment of skin infections with penicillin spray was therefore actively pursued at a Military Hospital for Skin Diseases, but though the results appeared promising and a considerable saving of time spent in hospital was claimed, the difficulty of assessment of therapy in conditions known to be self-limiting in character made it necessary to organize a properly controlled trial. The correlated clinical and bacteriological studies described in the present paper were therefore planned as part of a therapeutic trial and were designed to elucidate as far as possible the factors responsible for success or failure in individual patients. Clinical observations were made by J. H. T. D., bacteriological studies were carried out by K. D., and the research was directed by C. H. S.-H.

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Selection and Nature of Clinical Material

The clinical material comprised a good cross-section of the common types of skin disease of a predominantly infective nature found in soldiers in home and overseas stations. Efforts were indeed made to transfer patients with impetigo to the hospital from elsewhere, but the majority of the cases were admitted directly from units or from reception stations. Most patients had been ill for one to two weeks prior to the commencement of controlled therapy. At an early stage of the investigation, it was found that some patients responded rapidly to penicillin and others did not. Every effort was therefore made to categorize the patients on a constitutional and historical basis and to delineate clinical varieties. Five clinical types (see Plate 10) were discerned and the following brief description of these includes the numbers encountered among the 182 patients whose treatment is considered below.

Annular impetigo (17 cases). Cases in which a bulla was the essential lesion and healing occurred centrally at the same time as the periphery extended centrifugally. The disease appeared to correspond with the type traditionally referred to by dermatologists as 'staphylococcal impetigo' (Fox, 1864; Lewandowsky, 1922). Lesions usually occurred on the face, but might also be present on the trunk or limbs.

Sigilliform impetigo (12 cases). Cases with lesions consisting of 'stuck-on' dried crusts of exudate on a reddened infiltrated base and corresponding to the 'streptococcal impetigo' of Lewandowsky's classification. Lesions were frequently present on the eyebrows, the mid-line of the back of the neck, and the scalp.

Ecthyma (15 cases). Crusted lesions on the extremities of an ulcerative type which occurred either spontaneously or as a complication of scabies. At times, ecthyma-like lesions on the extremities were found in patients with sigilliform impetigo and, rightly or wrongly, such cases were included in the group with ecthyma only.

Furunculosis (6 cases). Cases with multiple furuncles.

Impetiginized seborrhoea and seborrhoeic dermatitis (132 cases). This group of conditions comprised by far the largest number of patients referred for treatment and undoubtedly constitutes the essential problem of infective skin disease in the Army. Although it was at first thought that patients with lesions of an undoubtedly seborrhoeic character could readily be distinguished from others with impetigo, it became more and more difficult as the investigation proceeded to draw sharp lines of differentiation. All cases in which the lesions were not strictly monomorphous, but included erythematous, macular, or papular rashes, pustules, diffuse scaling, eczematoid vesiculation, or diffuse superficial exudation were therefore grouped in this category. Cases with impetigo-like manifestations but with scaly, erythematous, or exudative lesions elsewhere, or which developed seborrhoeic lesions after healing of an impetigo, and cases of infective dermatitis of the digits were also included.

Bacteriological Findings

Prior to the commencement of therapy, a series of aerobic cultures was made by direct plating of exudate which oozed from the lesions after removal of the surface crust or by cultivation after moistening with broth if the skin was dry. Specimens were taken from both sides of the face or body where the two sides received different therapeutic applications, and in a limited number of cases from the anterior nares and from an unaffected area of skin on the chest or on the side of the nose. Primary cultures were made on 5 per cent. horse blood agar and also on a similar medium containing 1 : 500,000 crystal violet (Garrod, 1942) for the isolation of haemolytic streptococci. Subcultures from single colonies were made in the form of linear streaks on a nutrient agar containing 25 per cent. human plasma (Penfold, 1944). A strip of filter-paper moistened with penicillin solution containing 25 Oxford units per c.c. was then applied at right angles to these linear inocula. This technique, which was suggested by Major S. T. Cowan, R.A.M.C., permitted simultaneous observation of penicillin-sensitivity and coagulase production. The majority of cases were re-examined after 3, 7, 14, and 21 days of treatment and finally on discharge. In cases receiving penicillin, specimens taken during the period of therapy were cultivated on media to which penicillinase (Duthie, 1944) had been added. In addition to the record thus obtained of the aerobic flora of the lesions before, during, and after treatment, it was hoped that the examination of the relative sensitivity to penicillin of the organisms thus recovered would illuminate the response to therapy. As well as producing coagulase, some of the strains of *Staphylococcus pyogenes* isolated formed a diffusible fibrinolytic agent (fibrinolysin), which later dissolved the halos initially produced by coagulase activity round the growths on plasma sugar. Streptococcal typing to determine the Lancefield group was undertaken in 24 strains of haemolytic streptococci. Twenty-three belonged to Group A and one was Group C. The majority of the haemolytic streptococci were probably of Group A as found by Bigger and Hodgson (1943) in strains from cases of impetigo.

Tables I and II indicate the bacteriological findings before, during, and after treatment in 200 cases classified without reference to the type of therapy. Coagulase-positive staphylococci (*Staphylococcus pyogenes*) and β-haemolytic streptococci predominated and accounted for the flora in most cases before treatment. Coagulase-negative staphylococci, *Streptococcus viridans*, diphtheroids, and coliform organisms were occasionally present, but were numerically unimportant. The relationship between the type of flora and the clinical classification is shown in Table I. There appeared to be a relationship between the flora and the character of the lesions in cases of impetigo, which supported the traditional classification of staphylococcal and streptococcal varieties. Whereas the annular or circinate lesions usually yielded staphylococci only, those of the sigilliform variety yielded both staphylococci and streptococci. There was, however, no evidence to

support the contention of Bigger and Hodgson (1944) that the haemolytic streptococcus is a secondary invader of the lesions of impetigo. Fresh crusted lesions as often yielded haemolytic streptococci as did more aged lesions, and haemolytic streptococci rarely appeared in lesions at a second examination when they were absent initially. Table II indicates the remarkable degree

TABLE I

Relationship of Bacterial Flora to Clinical Classification

Clinical group	*Staphylococcus pyogenes* alone	Haemolytic streptococci alone	Both staphylococci and haemolytic streptococci	Neither staphylococci nor haemolytic streptococci	Total
Annular impetigo	17	0	2	0	19
Sigilliform impetigo	0	0	18	0	18
Ecthyma	0	6	5	0	11
Furunculosis	4	0	0	0	4
Impetiginized seborrhoea and seborrhoeic dermatitis	81	0	66	1	148
Total	102 (51 %)	6 (3 %)	91 (45·5 %)	1 (0·5 %)	200

TABLE II

Bacterial Flora Before, During, and After Therapy

	Initially	Up to 14 days of therapy	After 14 days or more of therapy	Healed skin on sites of lesions
Numbers of cases examined	200	155	46	81
Percentage incidence of *Staphylococcus pyogenes*	97	70	69	65*
Percentage incidence of haemolytic streptococci	42	22	35	11†

* If cases in which only a very scanty growth was obtained are excluded, this figure becomes 46.

† Only a scanty growth of haemolytic streptococci was usual from the healed skin.

of persistence of the cocci in the lesions of those cases in which repeated cultivation was performed. This matter will be discussed later in relation to the response to therapy. The examination of unaffected areas of skin indicated an abnormally high carrier rate for *Staphylococcus pyogenes*, but not for haemolytic streptococci. The skin of the chest yielded staphylococci in 33 of 111 cases and that of the side of the nose in no less than 50 of 83 cases. These carrier rates of 30 and 60 per cent. are higher than those recorded and reviewed by Miles, Williams, and Clayton-Cooper (1944) for the skin of normal subjects, in whom the maximum rate was 24 per cent. On the other hand, only two of 111 chest swabs and nine of 83 swabs from the outside of the nose yielded haemolytic streptococci, and carrier rates of up to 10 per cent. have been recorded for haemolytic streptococci by some workers (Hare, 1941). The swabs from the interior of the nose yielded normal carrier rates for *Staphylococcus pyogenes*, but an abnormally high incidence of haemolytic streptococci. Thus 49 of 120 cases yielded nasal staphylococci, which is

slightly lower than in the normal population examined by Miles, Williams, and Clayton-Cooper (1944), who found a mean carrier rate of 47·4 per cent. Eight of 120 swabs yielded haemolytic streptococci and this incidence contrasts with the infrequency of nasal as opposed to nasopharyngeal carriage of streptococci in normal persons (Straker, Hill, and Lovell, 1939).

The bacteriological findings may thus be summarized by the statement that the *Staphylococcus pyogenes* and haemolytic streptococcus either alone or together were usually found in the lesions of infective dermatoses, that they frequently persisted in the lesions throughout the period and even after completion of therapy, and that these organisms were encountered either on unaffected areas of skin or inside the nose in a significantly higher percentage of the patients with these skin diseases than in normal subjects.

Therapeutic Results

Penicillin applied locally. The major part of the present work has consisted of an assessment of the effects of treatment with penicillin applied locally. In order to control penicillin treatment by results obtained in similar cases with more orthodox remedies, the first group of patients who often had symmetrical lesions on the two sides of the body were treated on one side with control remedies and on the other side with penicillin (Harlequin technique). The number of days taken to obtain healing on the two sides of the body was noted and compared. In order to exclude the possibility that the poor contrast generally obtained was due to cross-infection or cross-transfer of medicament, the next group of patients received penicillin on all the lesions. The results were substantially the same. Finally, random allocation of patients according to the first letter of the surname enabled a series of patients wholly treated with penicillin or with control remedies to be compiled. Patients L to Z then received penicillin, while those in A to K category received control treatment. Again, the time taken to obtain healing was chosen as being the only objective measure of the effect of treatment. An arbitrary time-limit of 14 days was maintained throughout the trial and if healing was incomplete in 14 days the patient was transferred from the care of the investigators and treatment was changed. In the case of the Harlequin series the remedies were continued on the two sides for at least 14 days after healing occurred on one side, except when neither side healed within 14 days, in which case the experiment was abandoned. The method of application of penicillin was that of spraying on a solution containing 1,000 units per c.c. in distilled water with a special glass sprayer (MacKenna, 1944). Spraying was repeated at four-hourly intervals throughout the day and night in most cases, but the 2 a.m. application was sometimes omitted. A penicillin cream (Roxburgh, Christie, and Roxburgh, 1944) containing 500 units per gm. was used on nine patients, but because of unfavourable results, such as aggravation of primary lesions in cases of seborrhoea with impetigo-like manifestations, its use was discontinued.

Wet dressings of penicillin containing 200 units per c.c. were tried in two cases and application of penicillin by iontophoresis in five more cases, but neither method was sufficiently encouraging to warrant further use. In general, the penicillin spray was applied without removal of crusts unless the initial state necessitated a starch poultice, but in five cases crusts were

TABLE III

Penicillin Spray (Harlequin Technique). Days Required for Healing

	Annular impetigo		Sigilliform impetigo		Ecthyma		Furuncu-losis		Impetiginized seborrhoea and seborrhoeic dermatitis			
Number of cases	8		2		4		5		51			
Treatment abandoned*	—		—		—		2		19			
	P	C	P	C	P	C	P	C	P	C	P	C
Treatment	4	12	6	10	12	14	6	6	10	4	5	15
	8	15	11	21	7	7	5	14	13	15	4	12
P = Penicillin	4	4			11	9	14	14	7	9	6	6
	7	6			14	8			6	9	6	6
C = Control	6	6							10	8	14	14
	4	14							7	7	9	9
	4	12							11	18	8	8
	5	10							5	11	8	8
									8	8	12	12
									14	14	8	8
									6	6	10	10
									4	4	8	8
									5	6	18	4
									8	21	6	6
									9	9	7	6
									5	19	18	10
Average†	5·25	9·9	8·5	15·5	11·0	9·5	8·0	11·3			8·6	9·7
Difference between means	4·625										1·094	
Standard error	1·449										3·139	

* Neither treatment cured in 14 days.
† Excluding abandoned cases.

removed and an emulsifying base applied before spraying in order to retain the solution on the skin. Control medicament was varied to suit the particular type of case. Eau d'Alibour, gentian violet, penicillin solution or ointment inactivated by heat, lanette-wax ointment without penicillin, and silver nitrate were used on the various patients.

Tables III, IV, and V detail the results in all three series of patients treated locally. Table III describes 70 patients treated by the Harlequin technique in whom the number of days taken to heal with penicillin therapy (P) was compared with the days of healing with control remedy (C) in the same patient. The figures suggested that penicillin effected a more rapid rate of healing than control remedies in both varieties of impetigo and that in the entire group some advantage occurred to the penicillin-treated lesions. On the other hand, ecthyma was not benefited and both in furunculosis and seborrhoeic conditions some cases completely failed to heal with either

remedy in 14 days. Only in one or two instances did healing of the penicillin-treated lesions take an appreciably longer time than healing with the control remedy. Thus in the 70 patients, treatment with penicillin was abandoned 21 times, it was better than the control remedy 20 times, was of equal value 21 times, and was actually inferior in only eight instances. Table IV

TABLE IV

Penicillin Spray (Uncontrolled Group)

	Annular impetigo	Sigilliform impetigo	Ecthyma	Furunculosis	Impetiginized seborrhoea and seborrhoeic dermatitis
Number of cases	6	6	4	1	52
Treatment abandoned	—	—	1	—	21
Average duration in days*	5·6	9·0	11·6	7·0	8·5

Overall average excluding abandoned cases—8·3 days.

* Excluding abandoned cases.

TABLE V

Penicillin Spray (Controlled Group)

		Annular impetigo	Sigilliform impetigo	Ecthyma	Impetiginized seborrhoea and seborrhoeic dermatitis
Control therapy (A to K)	Number of cases	2	1	4	46
	Treatment abandoned	—	—	2	7
	Average duration of healing (days)*	4·0	8·0	7·5	8·1
Penicillin therapy (L to Z)	Number of cases	1	3	3	13
	Treatment abandoned	—	—	—	5
	Average duration of healing (days)*	7·0	7·0	12·6	9·1

Total average (days)

Control 7·4

Penicillin 9·8

Treatment abandoned

Control 9

Penicillin 5

* Excluding abandoned cases.

includes the 69 cases wholly treated with penicillin spray and shows little difference in average rate of healing of lesions compared with the healing-time of the penicillin-treated lesions in the Harlequin series. Table V gives details of the remaining 43 patients, chiefly with seborrhoeic conditions, who were allocated at random for treatment either with penicillin or with control remedies. The results suggest a slight superiority of control remedies, but the fact that fewer patients treated with penicillin (5) were abandoned compared with the control treatment (9) probably affected the average duration of healing, and it was not believed that the overall results were really different from those in the earlier series.

In all groups, instances of worsening of the condition while under treatment were rarely encountered, though the control medicament caused such an effect at times. One or two cases treated with penicillin developed an

erythematous eruption on the neck and shoulders which was at first attributed to penicillin sensitization. This was not indicated, however, by patch tests and it was finally considered that the rash was a manifestation of an underlying seborrhoeic state.

Relapses occurred in 21 patients, eight after discharge from hospital and 13 patients prior to discharge after initial healing. Relapses occurred chiefly in cases with seborrhoeic conditions, and two cases initially with lesions of annular impetigo developed relapses with lesions of acute seborrhoeic dermatitis. As relapse occurred six times in patients wholly treated with penicillin it could not be considered in the case of Harlequin-treated patients to be due to failure of the control remedy to eliminate the infection.

Early but unsustained healing occurred at times, particularly in cases of impetiginized seborrhoea or seborrhoeic dermatitis treated with penicillin, and such an effect is probably responsible for the view expressed by other workers that penicillin, though producing benefit in cases with seborrhoeic manifestations, fails to affect the underlying seborrhoeic state.

Penicillin by injection. Two small groups of patients received penicillin by intramuscular injection and this was unaccompanied by local therapy in six instances and reinforced by local spray in seven others. In the former group, 400,000 units were given daily in six injections, two of 100,000 and four of 50,000 units, and treatment was continued for seven days. Dramatic effects were not seen in these patients, who comprised one case each of carbuncle, annular impetigo, sigilliform impetigo, and ecthyma, and two of seborrhoeic conditions. The second group of patients received intramuscular penicillin at the rate of 50,000 units three-hourly for four days and also penicillin by spray. They comprised one case each of erysipelas and annular impetigo, two of sigilliform impetigo, and three of seborrhoea. The results were dramatic in the case of erysipelas, good in three other cases including two of impetigo and one of seborrhoea which all healed in five days, and poorer in three remaining cases. In view of the expenditure of penicillin entailed the method was clearly not worthy of general application at the present time.

Discussion

The therapeutic results obtained with penicillin administered locally were not only disappointing, but seemed to conflict with previously published work. In order to compare our results with those of other workers, Tables VI and VII were compiled by consolidation of the healing times of lesions treated with penicillin or control remedies. An average duration of healing in all forms of impetigo of 6·6 days with penicillin and 9·7 with control remedies was thus obtained. The 12 cases of impetigo treated by Roxburgh, Christie, and Roxburgh (1944), eight of which were in children and which included both staphylococcal and streptococcal infections, were healed in an average of eight to nine days with penicillin ointment, that is, in a longer time than in our cases. The apparent superiority of our results could have been due to

clinical separation of a particularly responsive group and allocation of the remainder to the seborrhoeic category. However, even in the cases of seborrhoea (Table VII), penicillin effected healing in 8·6 days on an average. The results of Taylor and Hughes (1944) referred chiefly to sycosis barbae and furunculosis. In seven cases of impetigo, healing was obtained in four

TABLE VI

Average Duration of Healing in Impetigo (Days)

	Annular impetigo	Sigilliform impetigo	All impetigo lesions
Penicillin	5·33 (15)	8·363 (11)	6·615 (26)
Control	8·7 (10)	13·0 (3)	9·692 (13)
Difference	3·367	4·637	3·077
Standard error	1·368	3·355	1·432

Figures in parentheses represent numbers of cases and half-cases of the Harlequin series.

TABLE VII

Treatment of Cases of Seborrhoea

	Totals*	Treatment abandoned (more than 14 days)	Healed	Average time for healing
Penicillin	116	45 (39 %)	71	8·6 days
Control	67	26 (39 %)	41	9·3 days

* Numbers of cases plus numbers of half-cases treated with Harlequin method.

to five days, but four cases relapsed. Our results in impetigo treated with penicillin therefore do not appear to be significantly different from the published results of other workers. It is in the large group of cases loosely classified as seborrhoea with impetigo-like manifestations and seborrhoeic dermatitis that the introduction of controls indicates a real failure of penicillin to achieve a satisfactory result. Penicillin therapy has achieved such outstanding success in many conditions that few reports thus far have considered in detail possible causes of failure. As the present investigation included attempts to elucidate the factors governing success or failure in individual cases, these must now be considered.

Sensitivity of organisms. All of 97 strains of haemolytic streptococci and all but 11 of 193 strains of *Staphylococcus pyogenes* recovered before treatment were fully sensitive to penicillin. Of the 11 patients with insensitive staphylococci on admission, two had received penicillin in previous therapy so that the actual incidence of penicillin-resistant organisms prior to the use of penicillin was 4·6 per cent. These resistant organisms were tested only by the plate method, employing a strip of paper soaked in penicillin containing 25 units per c.c. so that their resistance to higher concentrations of penicillin is unknown. However, the therapeutic results in the patients with initially resistant cocci were poor and 10 of the 11 patients resisted healing for more than 14 days. In a further 29 patients resistant strains of staphylococci not present initially appeared in the lesions during or after therapy and the frequency with which resistant staphylococci were encountered increased with increase in duration of therapy. The therapeutic results in these

29 patients were also poorer than the average, and only three healed within the time-limit of 14 days. The development of resistance to penicillin on the part of the staphylococci present in the lesions was thus one possible cause of therapeutic failure, but it did not account for the poor results in other patients who did not respond to therapy yet had fully sensitive

TABLE VIII

Comparison of Persistence of Bacteria in Lesions Treated with Penicillin Compared with Controls

	Lesions treated with control remedies	Lesions treated with penicillin
Percentage of cases in which *Staphylococcus pyogenes* present initially was found again at least on one second occasion after three days' treatment.	99 (72)	90 (143)
Percentage of cases in which haemolytic streptococci present initially were found again at least on one second occasion after three days' treatment.	67 (31)	56 (68)

Figures in parentheses refer to total number of lesions on which percentages were calculated.

organisms in lesions throughout the course of therapy. Nevertheless, the general phenomenon of development of resistance to penicillin appears worthy of further investigation, particularly in relation to the pathogenicity of the cocci. Spink, Ferris, and Vivino (1944) consider that such acquired resistance is accompanied by diminished pathogenicity. However, our own insensitive strains were capable of active coagulase production and this metabolic property has hitherto been considered to be correlated with pathogenicity (Miles, Williams, and Clayton-Cooper, 1944). Furthermore, some of the insensitive strains were actively fibrinolytic.

Persistence of organisms. Repeated swabbing of lesions during and after treatment showed that both staphylococci and streptococci persisted in the lesions, sometimes in reduced, but sometimes in apparently undiminished numbers in spite of treatment until healing was complete (Table I). Table VIII shows that organisms persisted almost with equal frequency in lesions treated with penicillin as in those treated with control remedies. The persistent organisms were, in the majority of instances, fully sensitive to penicillin and the reason for their persistence was not clear. It seemed that so long as the lesion was active and unhealed, whether it was apparently responding to penicillin or not, cocci were usually demonstrable. Thus in 22 rapidly healing lesions cured in under 10 days, 16 after three days treatment still had cocci in the lesions, and after seven days when the lesions consisted of little more than scales the cocci were found in only three of 10 cases. In 25 lesions not responding to therapy, 22 still had cocci after three days' treatment and 23 yielded cocci after seven days' treatment. Whether or not the persistence of organisms was significant as a factor preventing response to treatment and ultimate healing, underlying reasons for its occurrence appeared of some

interest and importance. Survival could have been due to the following causes:

Inadequate dosage of penicillin. Exudate was collected from lesions at periodic intervals after spraying and was found to contain amounts of penicillin ranging from approximately 0·5 to 15 units per c.c., depending on the length of time after spraying. Such exudate when sealed in capillary tubes and incubated remained clear and was sometimes sterile on subculture, whereas exudate from lesions not treated with penicillin developed visible colonies of cocci. When the fluid exuding from the penicillin-treated lesion was cultivated by immediate plating a growth of staphylococci or streptococci was usually obtained in spite of the content of penicillin originally present. Bigger (1944) has suggested that the organisms which persist in lesions treated with penicillin are in a dormant undividing stage unaffected by penicillin. Such a hypothesis, though attractive, does not take into account the active cellular defence of the body, and it is difficult to see why the resting cocci should not be eliminated by phagocytes or by antibody mechanisms.

Though the surface exudate from lesions appeared to contain therapeutically adequate amounts of penicillin it was not possible to investigate the depths of the lesion. The fact that the lesions of patients treated with full doses of penicillin by intramuscular injection were also not sterilized may simply indicate that the depths of the lesions cannot even be reached readily from the blood. Hirshfeld, Pilling, Buggs, and Abbott (1944) have also noted the persistence of bacteria in grafted burns in patients treated with penicillin, though they found that the grafts took successfully in a high proportion of cases.

Reinfection. Reinfection from other patients could not be demonstrated or ruled out in the absence of serological or bacteriological typing. Reinfection from other parts of the body seemed to be a possible cause of persistent organisms. The carriage of staphylococci on an unaffected area of the face was abnormally frequent and may indicate that the skin is more readily colonized by cocci in these patients than in normal subjects. Streptococci carried in the nose were an additional possible source of persistent infection in others, but neither in the case of streptococcal nor of staphylococcal carriage on normal areas of the body was there a clear relationship between such carriage and the therapeutic results. It seemed, in general, to be likely that reinfection from foci in the depths of the lesions provided a constant source of new organisms in spite of repeated applications of penicillin to the surface.

Lack of relationship between organisms and disease. The present investigation has suggested that a relationship exists between clinical types of infection and response to penicillin therapy. It is therefore probable that clinically different types are caused by the interaction of different aetiological factors. Thus impetigo is often regarded as a contagious disease, particularly in children, whereas seborrhoeic conditions are believed to be

related in some way to the constitution of the individual. Even in impetigo, the exact role of the bacteria found in the lesions is uncertain. Bigger and Hodgson (1943) were unable to satisfy themselves that the aetiology of impetigo was purely bacterial, but concluded that impetigo was due to the conjunction of infection with some hypothetical factor. It is difficult to dismiss the bacteria present in the lesions as mere secondary invaders, though they belong to the class defined by Wright (1923) as serophytes, which grow readily in fresh serum. That the response to penicillin is not governed simply by the relative importance of the factor of infection is shown by the more favourable results obtained in annular (staphylococcal) impetigo than in the sigilliform (streptococcal) variety. The unknown factor of the seborrhoeic state is clearly another factor which combines with that of infection to produce a condition which is resistant to treatment with bacteriostatic or bactericidal substances. Our conclusions are not very different from those of Sheehan and Fergusson (1943), who found that the success of various therapeutic substances in impetigo cases was unrelated to the bacteriological findings. Much further study of the aetiological factors involved in infective conditions of the skin is clearly needed.

Conclusions

1. Penicillin administered locally by spraying a solution containing 1,000 units per c.c. on to the lesions of various infective diseases of the skin was therapeutically superior to other remedies in a relatively minor percentage of such cases as are commonly encountered in the Army.

2. Penicillin spray was effective chiefly in impetigo and specially in annular (staphylococcal) impetigo. It was occasionally more effective than other remedies in cases of furunculosis or seborrhoeic conditions, but such an effect was unpredictable. It was less effective than other remedies in ecthyma. It was rarely, if ever, capable of producing harmful reactions.

3. Having regard to the expenditure of penicillin, no more effective method of administration was found than that of local spray.

4. Success or failure of therapy could not be correlated with the bacteriological flora except that the presence of penicillin-resistant organisms before therapy appeared to be associated with poor results. Development of penicillin-resistant organisms in the lesions during therapy was also in some of the cases a possible cause of therapeutic failure. Failure of penicillin therapy may also be due to inaccessibility of organisms in the depths of the lesions, or to the fact that the disease is often due to the interaction of aetiologically different factors. The hypothetical cause of the seborrhoeic state is one such factor.

Summary

1. The efficacy of treatment of pyoderma with penicillin as compared with other remedies was studied in a series of soldiers suffering from this disease. The conditions treated included seborrhoeic dermatitis and impeti-

ginized seborrhoea, annular (staphylococcal) impetigo, sigilliform (streptococcal) impetigo, ecthyma, and furunculosis.

2. Penicillin was in most cases applied as an aqueous spray containing 1,000 Oxford units per c.c. In one group of patients penicillin spray was administered to the lesions on one side of the body, and the results compared with those of other remedies applied to the lesions on the opposite side. In a second group of patients all the lesions were sprayed with penicillin and the results compared with a control group receiving other forms of treatment. Lastly, a small group of patients received large doses of penicillin by intramuscular injection (400,000 Oxford units daily).

3. Only in annular (staphylococcal) impetigo was penicillin markedly superior to other remedies. Cases of this disease formed but a small proportion of the cases of pyoderma encountered. In seborrhoeic dermatitis, which was the main type of pyoderma treated, penicillin was no more effective than other remedies. In some cases of this disease penicillin gave very good results, but these were unpredictable, and in others penicillin appeared less efficient than other modes of treatment. However, in no case was penicillin shown to be actively harmful. In ecthyma penicillin compared poorly with other remedies.

4. The exudate obtained from the lesions was examined bacteriologically before, during, and after treatment. Culture of the exudate resulted in the isolation of staphylococci (coagulase positive) or haemolytic streptococci, or both these organisms together, in 99·5 per cent. of the cases examined (200 in all). All the strains of streptococci (isolated from 97 cases) and the vast majority of the staphylococci (in 182 out of 197 cases) originally isolated from the lesions were sensitive to penicillin.

5. Success or failure of therapy could not in general be correlated with the flora isolated. In spite of treatment penicillin-sensitive organisms were usually recovered from the lesions after three days of treatment. In some cases penicillin-resistant staphylococci appeared during treatment and this phenomenon increased in frequency as treatment was prolonged. These cases, as well as the few in which penicillin-resistant organisms were initially present, were on the whole refractory to penicillin treatment. The development, or initial presence, of penicillin-resistant strains of staphylococci in the lesions was not the general cause of resistance to penicillin treatment, since in many refractory cases fully sensitive staphylococci were repeatedly recovered from the lesions after prolonged spraying as well as after intramuscular therapy. All strains of haemolytic streptococci isolated from the lesions both before and after penicillin treatment were sensitive to penicillin.

This investigation was planned and executed as a result of the interest and help of Major-General L. T. Poole, Director of Pathology, the War Office, and of Brigadier R. M. B. MacKenna, Consultant in Dermatology, the War Office, to whom we tender our sincere thanks.

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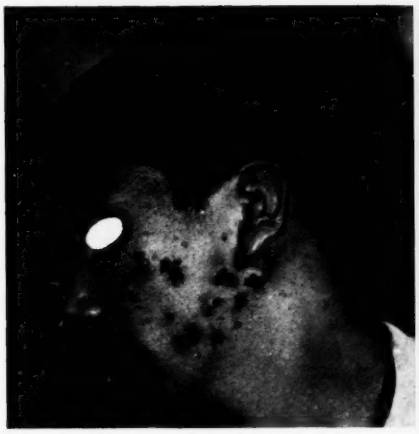

FIG. 1. Classical case of 'streptococcal' impetigo

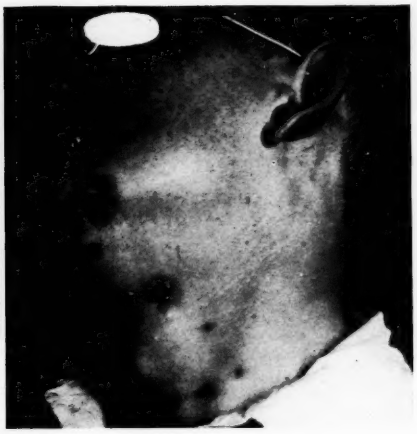

FIG. 2. Classical case of 'staphylococcal' impetigo

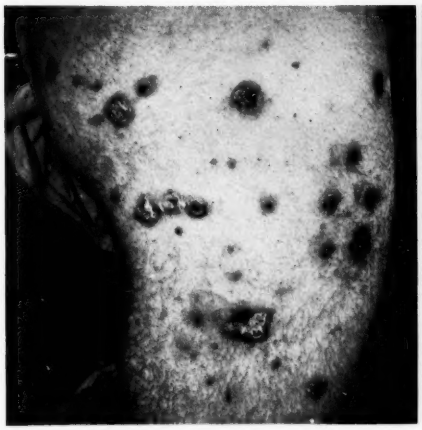

FIG. 3. Typical ecthyma

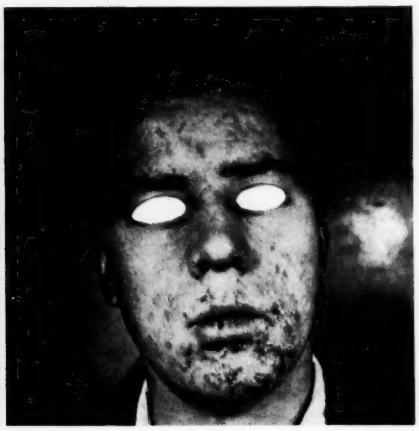

FIG. 4. Acute exudative seborrhoeic dermatitis

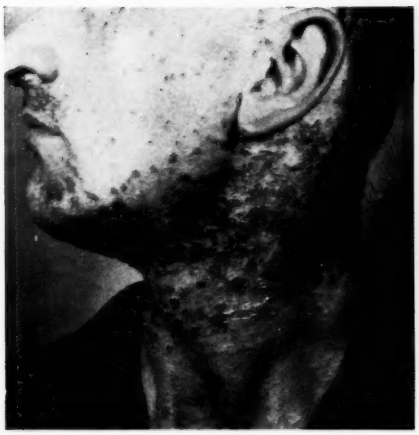

FIG. 5. Severe case of seborrhoeic dermatitis

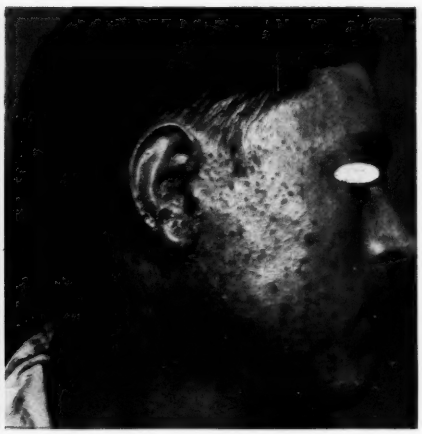

FIG. 6. Acute seborrhoeic dermatitis

612.129

THE NICOTINIC ACID CONTENT OF BLOOD IN HEALTH AND DISEASE[1]

By C. W. CARTER and J. R. P. O'BRIEN

(From the Department of Biochemistry, Oxford)

Two types of method, chemical and microbiological, have been used in the estimation of nicotinic acid and its derivatives in blood. Several of the chemical methods have as their basis König's reaction, in which the product of the fission of the pyridine ring by brom-cyanogen is condensed with a primary aromatic amine to yield a polymethine dye. There has been no general agreement among workers as to the amine most suitable for the development of this reaction. Aniline has been favoured by some (Swaminathan, 1938, 1939; Melnick and Field, 1940) and, in certain conditions (Melnick and Field, 1940), gives no colour with trigonelline or with pyroxidine. With this amine, nicotinamide gives a fraction of the colour obtained with nicotinic acid, but by hydrolysis it is readily converted to the acid. With *p*-aminoacetophenone (Harris and Raymond, 1939; Kodicek, 1940), the colour given by nicotinic acid is stated to be more intense than with aniline or *p*-methylaminophenol sulphate (metol), but its instability and its sensitivity to pH and salt conditions of the medium necessitate special precautions to ensure reproducible results. Metol has been used by Bandier and Hald (1939); it gives no colour with trigonelline or with pyridine and its derivatives. In its favour is the claim of Dann and Handler (1941) that it is more specific for nicotinic acid than aniline or *p*-aminoacetophenone.

The complications introduced into methods of estimation by chromogens other than nicotinic acid or its amide in urine and foodstuffs are serious, and even in the case of blood it cannot be said that they have been wholly eliminated. Further difficulties arise in attempts to ensure complete removal of non-specific pigments. The use of charcoal for the decolorization of urine and blood has proved satisfactory with some workers (Swaminathan, 1939; Melnick and Field, 1940), and unsatisfactory with others (Perlzweig, Levy, and Sarett, 1940; Dann and Handler, 1941). More elaborate procedures have also been adopted by Perlzweig, Levy, and Sarett (1940), and Wang and Kodicek (1943). Bandier (1941) employed tungstic acid to remove the colouring matter of blood. We have adopted this method in essentials and have obtained an almost complete removal of blood pigment and a satisfactory recovery of added nicotinic acid. It has been found necessary, however, to allow for the small amount of residual pigment by a blank determination, a procedure which is omitted by Bandier. The method has been

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employed in the determination of the total 'nicotinic acid' in blood in a series of 60 normal human subjects and 67 patients undergoing hospital treatment for a variety of clinical conditions.

Method

Five c.c. of blood are haemolysed with 35 c.c. of water in a 50 c.c. flask, and a drop of caprylic alcohol added to prevent frothing. Five c.c. of 10 per cent. (w/v) sodium tungstate followed immediately by 5 c.c. of 2/3 N-hydrochloric acid are added, the contents made up to the mark and thoroughly shaken. After 5 min., the precipitate is centrifuged off, and 30 c.c. of water-clear filtrate are pipetted into a small flask fitted with a condenser. After the addition of 5 c.c. of 10 N-sodium hydroxide, the contents are boiled gently for 1½ hrs. The contents of the flask with washings are transferred to a boiling tube, 5 c.c. of 2 per cent. (w/v) acid potassium phosphate added, and, after cooling, the pH is adjusted to 5·3 with 8 N-hydrochloric acid, using brom-cresol purple as external indicator. After adjusting the volume to 50 c.c. the small flocculent precipitate which appears is centrifuged off. Two 20 c.c. samples of the centrifugate are pipetted into boiling tubes, one of these being used to determine the extinction due to residual pigment. Both tubes are heated to 75° to 80° C. for 5 min. in a water bath, and into the tube for estimation of nicotinic acid, 2 c.c. of freshly prepared 4 per cent. (w/v) cyanogen bromide are run, and heating continued for a further 5 min. A control tube containing 20 c.c. of water with addition of 2 c.c. of cyanogen bromide is similarly heated. The tubes are then removed from the water bath, cooled, and the contents transferred to 25 c.c. flasks. To test and control flasks is added 600 mg. of metol, and after making up to 25 c.c. the mixtures are thoroughly shaken to dissolve all metol and then kept in the dark. The development of colour is complete within 30 min. The colour intensity of the test solution is measured in a Pulfrich photometer (filter S.43) against the control. At the same time the residual pigment of the blank solution is determined against water, and the value deducted from the test reading. The nicotinic acid content of the test solution can then be obtained by reference to a calibration curve for the instrument. Duplicate determinations on a large series of bloods indicate that the results obtained are reproducible with a mean error of ± 5·5 per cent.

Results

Concentration of nicotinic acid in the blood of normal subjects. Estimation of the nicotinic acid of whole blood was performed in a series of 60 subjects, all of whom on clinical examination appeared in normal health. The mean level for whole blood was 438 μgm. per 100 c.c. The Figure indicates that the normal range lies within the limits 260 to 573 μgm. per 100 c.c. of blood. Repeated determinations have been made over a period of 26 weeks in the case of two subjects, A and B, in the post absorptive state, who had lived

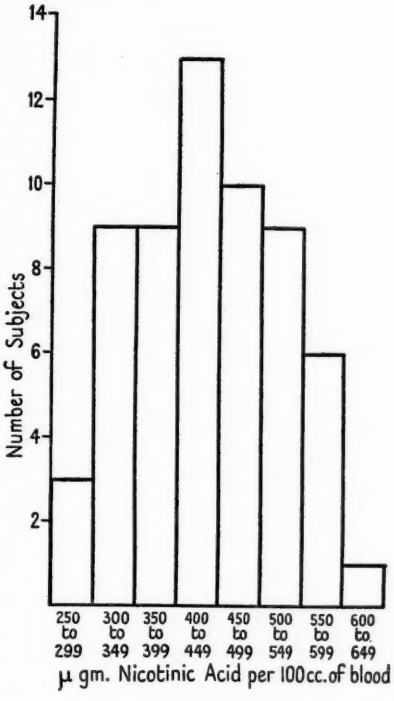
TABLE I

Nicotinic Acid Content of Blood at Various Times on Mixed Diet. Subject A

Date	17.9.41	16.12.41	18.12.41	29.12.41	14.1.42	30.3.42
Nicotinic acid μgm. per 100 c.c.	396	468	508	455	479	495

throughout on an ordinary mixed diet. With the exception of the initial value given for Subject A (Table I), the values appear to be constant within the limits of the experimental error.

It is generally agreed that the nicotinic acid present in the cells accounts for at least 95 per cent. of the normal content of whole blood, no doubt mainly bound as coenzymes. Absorption from the intestine of ordinary mixed meals appears to have little influence on the nicotinic acid level of blood. Ingestion of 100 mg. of nicotinamide by a post absorptive subject resulted in a rise in the red-cell content, but had little or no influence on that of the plasma. When larger doses (300 to 500 mg.) of the amide are ingested the rise in the blood level is considerable, reaching a peak within 30 to 60 min. and subsequently declining. At the same time there is a marked rise in the plasma level, which subsides rapidly within 2 hrs. (Table II). These results are similar to those reported by Melnick, Robinson, and Field (1940).



Nicotinic acid in whole blood of normal subjects.

Table III shows the effect of daily ingestion of 100 mg. nicotinic acid by one subject over a period of a week, and of ingestion of 15 mg. by 12 subjects over a period of 149 days. In five subjects in whom the initial level of blood nicotinic acid lay within the range 415 to 575 μgm. per 100 c.c., the mean rise after ingestion was 13 per cent., whereas for five subjects with an initial range of 260 to 350 μgm. per 100 c.c. the mean rise was 49 per

TABLE II

Changes in the Nicotinic Acid Content of Blood (μgm. per 100 c.c.) after Ingestion of Nicotinamide

Subject	Dose of amide (mg.)		Time (min.) after ingestion 0	15	30	45	60	90	120	135	180
A	100	Cells *	374	—	484	—	540	—	496	—	—
		Plasma †	42	—	37	—	58	—	22	—	—
B	300	Cells *	440	747	740	812	621	—	—	—	—
		Plasma †	23	136	142	118	147	—	—	—	—
C	500	Plasma †	0	—	199	—	—	88	—	20	21

* Cells in 100 c.c. blood. † Plasma in 100 c.c. blood.

TABLE III

The Effect on the Blood Nicotinic Acid (μgm. per 100 c.c.) of Ingestion of Nicotinic Acid for Prolonged Periods

Subject	Days after ingestion					
	0	7	25	46	63	149
1	383	532	—	—	—	—
2	417	—	687	594	475	—
3	448	—	489	—	552	—
4	573	—	656	—	510	521
5	469	—	—	656	573	500
6	431	—	—	375	469	354
7	260	—	389	—	542	469
8	344	—	—	—	479	—
9	344	—	—	—	364	531
10	312	—	500	433	562	448
11	385	—	542	—	396	—
12	323	—	652	427	425	469
13	396	—	750	—	—	—

TABLE IV

Concentration of Nicotinic Acid in the Blood in Disease

Subject	Case details	Nicotinic acid μgm. per 100 c.c. of blood
	Pellagra:	
1		238
2		464
3		362
	Wernicke's encephalopathy:	
1		482
2		396
	Sprue:	
1	Before treatment	145
	After treatment with 90 mg. nicotinic acid daily—2nd day	187
	11th ,,	338
	68th ,,	417
	Pernicious anaemia:	
1	Hb. 36% Red cells 1,800,000 per c.mm. C.I. 0·97	260
2	,, 20% ,, 820,000 ,, ,, 1·1	293
3	— — —	260
4	,, 48% ,, 1,740,000 ,, ,, 1·1	614
	Hypochromic anaemia:	
1	Hb. 40% Red cells 3,300,000 per c.mm. C.I. 0·6	359
2	,, 38% ,, 4,400,000 ,, ,, 0·4	437
3	,, 68% ,, 3,500,000 ,, ,, 0·97	573
4	,, 38% ,, 2,100,000 ,, ,, 0·9 (Pregnancy)	229
	Hyperthyroidism:	
	B.M.R. / Blood nicotinic acid (μgm. per 100 c.c.) before treatment	
1	+75 215	—
2	+23 251	—
3	+29 344	—
4	+34 330	—
5	+44 391	—
6	+42 330	—

Subject	Case details			Nicotinic acid μgm. per 100 c.c. of blood
	B.M.R.	Blood nicotinic acid (μgm. per 100 c.c.) before treatment		
7	+44	385		—
8	+36	344		—
9	+48	195	10 days iodine therapy	289
			10 „ after operation	687
10	+36	312	9 „ after operation	427
11	—	271	10 „ iodine therapy	289
			10 „ after operation	404
12	+35	34	10 „ iodine therapy	493
	Myeloid leukaemia:			
1	W.B.C. 306,000			693
2	„ 450,000			937
3	„ 300,000			704
4	—			721
5	„ 70,000			303
6	„ 74,000			302
	Lymphatic leukaemia:			
1	W.B.C. 5,000			315
2	„ 6,400			260
	Subacute combined degeneration of the cord:			
1				385
2				469
	Pregnancy:			
1	Normal 39 weeks			351
2	„ „ „			427
3	„ „ „			281
4	„ „ „			396
5	Toxaemia			440
6	Eclampsia			534
7	„			555
	Neuritis:			
1	Multiple			508
2	„			417
3	Toxic			385
4	Sciatica			583
5	„			646
	Hepatic disease:			
1	Infective hepatitis			521
2	„ „			375
3	Acute hepatic necrosis			416
4	Congenital haemolytic icterus			635
5	Carbon tetrachloride poisoning			343
	Ulcerative colitis:			
1				339
2				394
3				458
4				416
	Pulmonary tuberculosis:			
1				484
2				593
3				510
4				625

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cent. The mean upper limits reached for the two groups after ingestion were respectively 529 μgm. and 471 μgm. The results suggest that continued ingestion of nicotinic acid at the level indicated above results in the attainment of a degree of saturation in the blood which is limited by the ability of the blood cells to fix nicotinic acid as coenzymes.

Concentration of nicotinic acid in blood of abnormal subjects. The blood concentration of nicotinic acid in a series of hospital patients is shown in Table IV. We have had an opportunity of investigating only three cases of pellagra. In two chronic cases associated with insanity the nicotinic acid level was within the normal range, but in the other case the blood level was low. These findings are insufficient to justify any general conclusion, but they accord with the experience of Field, Melnick, Robinson, and Wilkinson (1941), who reported that the range of blood and plasma nicotinic acid in deficient subjects overlapped that for normally nourished individuals. Jolliffe, Bowman, Rosenblum, and Fein (1940) claimed that Wernicke's encephalopathy is associated with nicotinic acid deficiency, and that after nicotinic acid therapy the mortality was reduced from over 60 per cent. to 13 per cent. In two cases of encephalopathy we found normal blood levels. In one long-standing case of sprue the very low value of 145 μgm. rose over a period of 68 days to 417 μgm. as a result of daily ingestion of 90 mg. of nicotinic acid. This patient showed hyperkeratotic areas on both arms and legs, and patches of weeping eczema, together with a severe macrocytic anaemia. Neither the cutaneous lesions nor the anaemia appeared to improve as a result of nicotinic acid administration, and the condition was evidently not pellagrous. It seemed possible, however, that the low nicotinic acid level of the blood and the macrocytic anaemia were both associated with impaired absorptive function of the intestine. In three of four cases of pernicious anaemia the blood nicotinic acid was low. On the other hand three cases of hypochromic anaemia gave normal values. Bandier (1941) also reported low blood nicotinic acid values in two cases of pernicious anaemia. On the other hand, he found that in polycythaemia vera the blood level was high. In myeloid leukaemia with a great increase in polymorphonuclear cells there was a parallel increase in blood nicotinic acid in three cases, whereas in two cases in which the leucocytosis was less marked the blood nicotinic acid was subnormal. In two cases of lymphatic leukaemia with no increase in the peripheral white cell count the nicotinic acid values were also low. While no exact computation can be made from the data reported here, a rough calculation indicates that the white cell may contain some 10 times as much nicotinic acid as the erythrocyte. In 12 cases of hyperthyroidism with increase of basal metabolic rate from +23 per cent. to +75 per cent., low blood nicotinic acid values were found in nine subjects. In four of these the blood nicotinic acid was followed after treatment by iodine therapy or operation. Subjects 9, 10, and 11 had low initial values which rose to normal levels after treatment, while in the case of subject 12, who had a normal initial level, no change was observed after iodine treatment. In none of the

other clinical conditions studied, hepatic disease (4), pregnancy (7), ulcerative colitis (4), pulmonary tuberculosis (4), neuritis (5), cardiac failure (2), subacute combined degeneration (2), Vincent's angina (4), nephritis (2), diabetes mellitus (1), and acne rosacea (2) was there any evidence of abnormal blood nicotinic acid level.

Discussion

In Table V is recorded the range of nicotinic acid concentration in the blood reported in the literature, in normal subjects and in deficient states. Most authors who have employed a chemical method of estimation give a

TABLE V

Concentration of Nicotinic Acid in the Blood (μgm. per 100 c.c.) of Normal and Deficient Subjects

Author	Method	Normal subjects	Deficient subjects
Swaminathan (1939)	Bromcyanogen and aniline	330–530	—
Ritsert (1939)	,, ,,	330–460	—
Kühnau (1939)	,, ,,	250–450	80–180
Field, Melnick, Robinson, and Wilkinson (1941)	,, ,,	520–830	490–940
Bandier (1941)	,, and metol	320–450	—
Carter and O'Brien (1945)	,, ,,	260–570	240–460
Vilter, Koch, and Spies (1940)	*H. influenzae*	270–870	120–540
Kohn, Bernheim, and Felsovanyi (1939)	*H. parainfluenzae*	320–800	400–640
Querido, Lwoff, and Lataste (1939)	*B. proteus*	620–890	730–1,030
von Euler and Schlenk (1939)	Yeast fermentation	800	—
Axelrod, Madden, and Elvehjem (1939)	,, ,,	330–720	630

similar range of values for normal subjects. Field, Melnick, Robinson, and Wilkinson (1941) are exceptional in reporting substantially higher values, and their method of obtaining colourless filtrates for estimation may be open to criticism. The values obtained by microbiological methods of assay are higher and have a wider range. It may be questioned whether lack of specificity may not introduce a complication here. Two conclusions may, however, be drawn from the available data. In the first place quite wide variations in content of nicotinic acid in the blood of different individuals in normal health may occur. Secondly, the majority of the evidence relating to states of nutritional deficiency indicates that the range of blood nicotinic acid overlaps that found in normal subjects. The data reported in the present paper and elsewhere as to the variations in nicotinic acid content in several blood dyscrasias indicate that such variations may arise independently of variations in the body as a whole. Thus it appears that studies of blood nicotinic acid are of little value as a criterion of the state of nutrition in respect of this factor. In conditions of impaired intestinal absorption as in sprue, or associated with raised basal metabolism as in hyperthyroidism, low levels of blood nicotinic acid may occur without any clinical manifestations suggestive of pellagra. With regard to hyperthyroidism, it is of interest that a marked

decrease in the coenzyme content of rat liver and kidney cortex after thyroid feeding has been reported by Katzenelbogen, Axelrod, and Elvehjem (1941). Similarly Peters and Rossiter (1939) reported a fall in the cocarboxylase content of the brains of rats injected with thyroxin. The cozymase and cocarboxylase levels can be restored or maintained by feeding additional nicotinic acid or aneurin respectively, which suggests that the primary effect of induced hyperthyroidism is to increase the rate of coenzyme destruction, rather than to promote a decrease in its synthesis. While these results are of interest, it is not yet possible to correlate the depletion of coenzymes or change of cellular metabolism with the clinical features of pellagra (Handler and Dann, 1942). Finally, in none of the other clinical conditions studied was there any evidence of an abnormal blood nicotinic acid level.

Summary

1. Concentration of nicotinic acid has been determined in the blood of 60 normal subjects, and found to lie in the range of 260 to 573 μgm. per 100 c.c. of blood.

2. In two subjects repeated analyses showed that the blood concentration of nicotinic acid is constant over a period of time, but is temporarily increased after the administration of large doses of nicotinamide.

3. Prolonged administration of nicotinic acid appears to lead to the attainment of a degree of saturation in the blood which is limited by the ability of the blood cells to fix nicotinic acid as coenzymes.

4. The nicotinic acid concentration in the blood in a variety of pathological conditions does not greatly differ from normal values. Hyperthyroidism and sprue may be associated with low values. Myeloid leukaemia with a high polymorphonuclear count is associated with high nicotinic acid values. Pernicious anaemia may give low values, whereas in hypochromic anaemia normal values are observed.

5. It is concluded that the concentration of nicotinic acid in the blood does not provide a useful nutritional index.

We wish to thank Professor R. A. Peters for his interest in this work, Professor L. J. Witts and Drs. Gibson, Hobson, and Cooke for permission to study patients in their charge, and R. E. Mapes for valuable technical assistance.

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THE HEREDITARY AND FAMILIAL ASPECTS OF EXOPHTHALMIC GOITRE AND NODULAR GOITRE[1]

By LAURENCE MARTIN

(From Addenbrooke's Hospital, Cambridge)

With a genetical note by R. A. Fisher

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Introduction

The hereditary and familial aspects of exophthalmic goitre, although not entirely disregarded, have not apparently been closely studied in the past. They have most often received attention in connexion with the occurrence of exophthalmic goitre among children (Cockayne, 1928; Atkinson, 1938; Moolten and Bruger, 1942) while isolated families notably affected by the disease are also on record. (Wild, 1886; Pern, 1911; Souques and Lermoyez, 1919; Climenko, 1920; Morrison, 1928.) Such restricted studies have in general contributed little to our knowledge, for some have consisted at the most of a few spectacular family trees from which general genetical conclusions could scarcely be drawn, while others have been encyclopaedic reviews of the literature without providing any decisive information.

Joll (1932) stated that there was no real evidence that exophthalmic goitre was usually hereditary and Means (1937) could allow only that hereditary factors might be important in production of the disease. No detailed study of the families of a large series of adult exophthalmic goitre patients appears to exist, although Mackenzie (1916) noted affected relatives in 44 of 438 cases and Gardiner-Hill (1934) recorded six per cent. of 100 cases with a history of the disease in ascendants and nine per cent. with affected siblings. In the case of nodular goitre, whether non-toxic or associated with secondary thyrotoxicosis, any hereditary or familial factors are bound up with those of simple colloid goitre which is a prerequisite antecedent of a nodular goitre. As will be discussed later the factor of environment is so entangled with any possible hereditary trait that a clear separation of the two would be extremely difficult. The object of the present paper is to set out the results of a study of the familial and hereditary factors in an adult series of 90 cases of exophthalmic goitre (primary thyrotoxicosis) and 111 cases of nodular goitre, both toxic (secondary thyrotoxicosis) and non-toxic, and to examine the information obtained from both types of the disease.

[1] Received August 5, 1945.

Material

All the cases have been personally questioned and examined. Detailed family trees were obtained from 35 cases of exophthalmic goitre and 50 cases of nodular goitre, while details of any relatives affected by goitre were noted in the remainder. Information about possible consanguinity of the patients' parents is not available because it was not anticipated at the time of collection of data that statements of consanguinity might be valuable. On reviewing the results obtained, it is clear that such information might have been pertinent in connexion with the finding of a factor of recessive inheritance, if consanguineous marriages of the patients' parents had exceeded five per cent. The patients were all of the hospital class; 135 were drawn from the Borough of Cambridge, 55 from the adjacent urban and rural districts of Cambridgeshire, Isle of Ely, Hertfordshire, Suffolk, Essex, Norfolk, and Bedfordshire, 10 from London, and one from Scotland. The 174 woman patients were almost all occupied in their homes; only 25 had other work as clerks, shop-assistants, or domestic servants. Of the 27 male patients 17 were agricultural workers, while the remainder were artisans or shopkeepers and one was a railway signalman. All the patients were adults, and cases of puberty goitre were excluded from the series partly because evidence of thyrotoxicosis was often transient or doubtful and partly because of the difficulty in assigning such cases either to the primary or secondary category of thyrotoxicosis.

Cases of toxic and non-toxic nodular goitre have been included together under the description of nodular goitre for the following reasons:

(i) A simple colloid goitre is the starting-point of both types, hence any hereditary or familial trait is likely to be the same for each.

(ii) A definite diagnosis of thyrotoxicosis is frequently difficult in patients with a nodular goitre and there are many doubtful or borderline cases.

(iii) Thyrotoxic symptoms are liable to develop at any time in the possessor of a nodular goitre, and a certain proportion of these considered to be non-thyrotoxic at the time of examination might well become thyrotoxic at a later date.

The broad classification of patients into exophthalmic goitre and nodular goitre rested upon the history, clinical signs, and histological examination of the goitres from those submitted to thyroidectomy.

General Considerations

A study of this kind should ideally comprise examination of all the known relatives of each patient, but this was impracticable and reliance has necessarily been placed upon the patients' statements. In some instances several members of one family who were affected by goitres have been seen because they sought treatment at Addenbrooke's Hospital, and occasionally a relative who accompanied a patient to hospital was also found to have a goitre, but these chance occurrences were infrequent. Nevertheless, there are good grounds for believing what goitre patients say about their relatives in respect

of exophthalmic goitre in particular. A patient with exophthalmic goitre has striking outward appearances and is quick to observe or remember similar manifestations in a relative, so that a family history of exophthalmic goitre is usually reliable. A goitre is generally a fairly obvious phenomenon and it carries no stigma in lay minds so that, in contradistinction to insanity or tuberculosis, patients do not hesitate to volunteer information. Some patients knew that a relative had been operated upon for a goitre but did not know its type, while others could not go further than report a relative with a lump in the neck. In such instances exophthalmic goitre could be inferred or excluded by questioning, provided that the patient had actually seen the affected relative, but it was sometimes impossible to be certain whether a relative's goitre was toxic or non-toxic, although an operation on it suggested the former. It is evident that the reported number of affected relatives is likely to be smaller than the actual number, for small goitres are sometimes not obvious to laymen, as is shown by those found in patients who were unaware of their presence. There is also the unpredictable chance that the young and unaffected children of goitre patients might develop a goitre or thyrotoxicosis later in life.

Having regard to these considerations the following classification was adopted for the goitres of affected relatives:

Known exophthalmic goitre (Ex. G.)
Known toxic goitre (T. G.)
Known simple goitre (S. G.)
Goitre, not known to be toxic or presumed simple (G.).

The toxic goitre group probably included most cases of toxic nodular goitre in which exophthalmos is usually slight or absent.

Results

The results are derived from two sources, either from data from all the cases or only from those whose family trees were known. From the former, crude information is obtained concerning the number and relationships of the various relatives affected, and from the latter, more detailed information concerning siblings. Information about mothers and fathers could reasonably be accepted from all the cases whether full family trees were available or not.

Tables I and II show the numbers and relationships of the 88 affected relatives of 90 cases of exophthalmic goitre and 111 cases of nodular goitre. So far as they go the following deductions can be made:

(i) That female relatives are predominantly affected with goitre of all types by 75 females to 13 males among the total of 88 affected relatives.

(ii) Of the 75 affected female relatives sisters were most frequently affected (43), followed by mothers (15), aunts (10), and daughters (7).

(iii) Males were seldom affected; brothers 12 times, fathers once, and sons not at all. It was noteworthy that the eight affected brothers of exophthalmic goitre patients all had exophthalmic goitre, while the four affected

TABLE I

Crude Totals of Affected Relatives

	90 exophthalmic cases					111 nodular goitre cases				
	Ex. G.	T. G.	S. G.	G.	Total	Ex. G.	T. G.	S. G.	G.	Total
Mothers	—	1	5	—	6	—	2	2	5	9
Fathers	—	—	—	—	—	—	—	1	—	1
Sisters	8	2	3	3	16	1	7	8	11	27
Brothers	8	—	—	—	8	—	—	2	2	4
Sons	—	—	—	—	0	—	—	—	—	0
Daughters	—	—	—	1	1	—	2	3	1	6
Maternal aunts	—	—	—	3	3	—	—	—	1	1
Paternal aunts	1	—	—	1	2	1	—	1	2	4
Totals	17	3	8	8	36	2	11	17	22	52

TABLE II

Nature of Goitre in Affected Relatives

	Ex. G. and T. G.	S. G. and G.	Total
Relatives of 90 Ex. G. patients	20	16	36
Relatives of 111 nodular goitre patients	13	39	52

brothers of nodular goitre patients all had simple goitres or goitres not known to be toxic.

(iv) Patients suffering from exophthalmic goitre had more relatives with exophthalmic goitre than did patients with nodular goitres by 17 to 2.

(v) Patients with nodular goitres had more relatives with simple goitres or goitres which were not known to be toxic than did patients with exophthalmic goitre by 39 to 16.

(vi) The occurrence of toxic goitre, presumed not to be exophthalmic and probably to be secondary thyrotoxicosis, was commoner among the relatives of nodular goitre patients than among those of exophthalmic goitre patients by 11 to 3.

The trend of this information is to confirm general experience that women suffer from goitres of all types more frequently than men, and to suggest that patients with exophthalmic goitre tend to have relatives affected by it, whereas patients with nodular goitres more often have relatives affected by simple or nondescript goitres. As regards comparison with relatives of non-goitrous and non-thyrotoxic individuals, it may be said that a certain number of goitres of all types occur by chance throughout the general population. It is probable that simple goitres, smooth or nodular, would out-number exophthalmic or toxic goitres because of their more numerous causes such as residence in an area of endemic goitre and the influence of pregnancy or sex-epochs among women. It is therefore significant that the goitrous relatives of patients with exophthalmic goitre should have had exophthalmic goitre more frequently than simple goitre, and this suggests that a familial characteristic is present at any rate in some cases. Similarly, patients with nodular goitre had three times as many relatives with simple goitres or goitres which

were not known to be toxic than did those with toxic or exophthalmic goitres, but for reasons to be discussed later this cannot be directly attributed to hereditary rather than to environmental causes. Although no figures are available for the incidence of goitre among the relatives of non-goitrous persons, it seems improbable that they would approach those of Table I, which shows 88 goitrous relatives in the families of 201 goitrous patients.

Study of affected siblings from available family trees. Family trees were available from 35 patients with exophthalmic goitre and from 50 patients with nodular goitre. There was a history of goitre among the siblings of 15 patients with exophthalmic goitre and of 17 patients with nodular goitre. This represents an incidence of goitre among siblings in 43 per cent. of the families of exophthalmic goitre patients and in 34 per cent. of the families of nodular goitre patients. Nineteen (12 per cent.) of the 160 siblings were affected by goitre, namely, 13 sisters (16 per cent. of the total of 79 sisters) and six brothers (7 per cent. of the total of 81 brothers). The types of goitre affecting the siblings are shown in Table IV. Of the 19 affected siblings, therefore, no less than 14 had exophthalmic goitre, two had toxic goitres, and all the affected brothers had exophthalmic goitre. Of the 214 siblings of 50 patients with nodular goitre, 12 (6 per cent.) were affected by goitre, namely, nine sisters (8 per cent. of the total of 111 sisters) and three brothers (3 per cent. of the total of 103 brothers).

The types of goitre affecting the siblings are shown in Table VI. Of the 12 affected siblings 10 had goitres which were simple or not known to be toxic. There was no example of exophthalmic goitre, but two sisters had toxic goitres. Table VII shows that sisters of exophthalmic goitre patients were affected by exophthalmic goitre or toxic goitre in 10 cases out of 13, whereas seven of the nine affected sisters of nodular goitre patients had simple or nondescript goitres.

Table VIII shows that brothers were uncommonly affected by goitres of any kind, but those of exophthalmic goitre patients who were affected invariably had exophthalmic goitre. All the affected brothers of nodular goitre patients had simple goitres or goitres not known to be toxic. If the affected siblings of exophthalmic goitre patients are taken together, 14 out of 19 had exophthalmic goitre and two had toxic goitre, while those of nodular goitre patients included only two with toxic goitre and none with exophthalmic goitre. These results confirm the deductions drawn from the crude figures of Table I and tend to show that there is a familial tendency for the occurrence of both exophthalmic goitre and for nodular and simple goitre, and that these tendencies are distinct. A familial tendency in either type of goitre is clearly not the rule, for siblings were affected in only 43 per cent. of the families of exophthalmic goitre patients, and in 34 per cent. of the families of nodular goitre patients. Nevertheless, these are considerable incidences, and in the case of exophthalmic goitre there is evidence to follow that a tendency or liability to this disease may exist in apparently unaffected relatives.

TABLE III

Siblings of 35 Exophthalmic Goitre Patients

	Males	Females	Total
In the 15 affected families	32	35	67
In the 20 unaffected families	49	44	93
Totals	81	79	160

TABLE IV

Types of Goitre in Siblings of Exophthalmic Goitre Patients

	Ex. G.	T. G.	S. G.	G.	Total
Sisters	8	2	3	—	13
Brothers	6	—	—	—	6
Totals	14	2	3	—	19

TABLE V

Siblings of 50 Nodular Goitre Patients

	Males	Females	Total
In the 17 affected families	31	41	72
In the 33 unaffected families	72	70	142
Totals	103	111	214

TABLE VI

Types of Goitre in Siblings of Nodular Goitre Patients

	Ex. G.	T. G.	S. G.	G.	Total
Sisters	—	2	2	5	9
Brothers	—	—	1	2	3
Totals	—	2	3	7	12

Comparison of the Types of Goitres Affecting Siblings of Patients with Exophthalmic Goitre and Nodular Goitre

TABLE VII

	Ex. G.	T. G.	S. G.	G.	Total
Sisters of exophthalmic goitre patients	8	2	3	—	13
Sisters of nodular goitre patients	—	2	2	5	9
Totals	8	4	5	5	22

TABLE VIII

	Ex. G.	T. G.	S. G.	G.	Total
Brothers of exopthalmic goitre patients	6	—	—	—	6
Brothers of nodular goitre patients	—	—	1	2	3
Totals	6	—	1	2	9

Genetical Note by Professor R. A. Fisher

'Although no single-factor explanation can be accepted as a sufficient explanation even for exophthalmic goitre, one significant feature of the records is qualitatively of a kind to be expected from recessive inheritance and definitely opposed either to a purely environmental explanation or to

inheritance of dominant type; this is that in the pedigree record the proportion of sibs affected exceeds that of the parents. Sibs, it should be noted, are more likely to be missed through not yet having developed manifest symptoms and are not usually exposed to an environment more similar to that of the propositus than that of the parents. Yet the following tables[2] show a clear disproportion which is statistically significant in both sexes.

TABLE IX

Males

	Affected	Unaffected	Total
Brothers	6	75	81
Fathers	0	90	90
Totals	6	165	171

TABLE X

Females

	Affected	Unaffected	Total
Sisters	10	69	79
Mothers	1	89	90
Totals	11	158	169

TABLE XI

Totals

	Affected	Unaffected	Total
Offspring	16	144	160
Parents	1	179	180
Totals	17	323	340

In these tables the relatives noted as affected are those suffering from exophthalmic goitre, with whom have been included three cases of toxic goitre not positively known to be exophthalmic. These are one mother and two sisters. Even including these, however, the disproportionate frequency of affected sibs, as compared with parents, is clearly shown among the relatives of both sexes. No such contrast is to be observed among the relatives of patients suffering from nodular goitre, for example, for these 8 per cent. of mothers and 8 per cent. of sisters suffered from goitres, including all save exophthalmic cases in this classification. For exophthalmic therefore, though not for nodular goitre, there is evidence strongly suggestive of a single recessive factor favourable to the disease and perhaps necessary for its occurrence, but this does not mean that all recessives develop the disease. If this were so we should expect approximately one-quarter of the sibs to be affected and

[2] It should be noted that in these tables the mothers and fathers of all 90 cases of exophthalmic goitre are included because the information concerning them is considered to be reliable, but for the sibs, only those in the 35 families whose full trees are known are included. The 35 trees were influenced only by availability and not by any selection on account of defect. There is thus no reason to suppose that the proportions of affected and unaffected sibs would have been different had all 90 family trees been available.

the tabular material set out above may be taken, on this interpretation, to imply that among females about half the recessives, and among males about one-quarter, develop manifest symptoms.'

The present study, then, has provided evidence suggesting that the familial occurrence of exophthalmic goitre is due to the inheritance of a liability to the disease, but there is none favouring heredity in nodular goitre. It remains, therefore, to discuss the factors accounting for the familial occurrence of nodular goitre and to consider the conclusions concerning exophthalmic goitre in the light of pre-existing evidence for its hereditary transmission.

Factors in the Familial Occurrences of Nodular Goitre

The first point for emphasis is that nodular goitres (true adenomata excluded) are the outcome of simple goitres which almost universally become nodular with the passage of time. Thus discussion inevitably centres upon the causal factors of the initial simple goitre.

The role of iodine deficiency. Simple goitres may be either endemic or sporadic, and it seems probable that deficiency of iodine, either absolute or relative, is the basic cause of both, although this cannot be conclusively proved for sporadic goitres. Surveys in endemic goitre regions have, in general, shown that a dietary deficiency of iodine can be successfully correlated with the occurrence of goitre (McClendon and Hathaway, 1924; Hercus, Benson, and Carter, 1925; Hercus and Roberts, 1927) and that prophylactic administration of iodine to children in endemic goitre areas very greatly reduces the incidence of goitre (Marine, 1924; Hercus, Benson, and Carter, 1925). On the other hand, Orr (1931), from an iodine survey in areas of England and Scotland, could not show such a correlation. Nevertheless, he acknowledged the excellent results obtained in preventing goitre among children living in endemic areas by the administration of potassium iodide. The undeniably good results of prophylactic treatment carry great conviction, and the Goitre Sub-Committee of the Medical Research Council (1944) recently appealed for the addition of potassium iodide to table-salt as a national policy for the prevention of endemic goitre. It may therefore be accepted that an environmental and dietary deficiency of iodine causes simple endemic goitre.

Sporadic cases of simple goitre, on the other hand, cannot be explained on these grounds, for they occur in areas where iodine deficiency does not exist and in persons who are alone affected in a family or community living under the same conditions. A relative iodine deficiency has therefore been suggested in these cases, brought about by various agencies whose actions are at present unproven. Thus the simple goitres which not uncommonly occur during puberty or pregnancy in women are believed to be caused by demands for thyroxine, and so for iodine, which some thyroids cannot meet. The glands then undergo epithelial hyperplasia followed by permanent colloid

change, and a simple goitre results. Infections are also thought to be capable of causing a simple goitre by interfering with the normal absorption or utilization of iodine by the thyroid gland. Thus the main causes of simple goitre, whether known or suggested, are thought to be due to iodine deficiency in some form, dependent either upon environmental or individual factors.

The role of heredity. If a family lives in an endemic goitre area for several generations the majority of members may be expected to possess goitres by

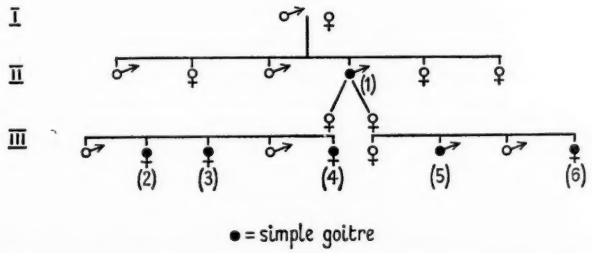

FIG. 1. The father (1), who came from non-goitrous stock, went to live at an early age in a mountainous district of Scotland where the drinking-water came from a running burn. He developed a simple goitre in early adult life and married twice. Both wives were non-goitrous and came from other parts of the country. By the first wife he had two sons and three daughters of whom the latter (2, 3, 4) developed simple goitres. By the second wife he had two sons and two daughters of whom one son (5) and one daughter (6) developed simple goitres. Three affected daughters (2, 3, 4) and one affected son (5) all married and left the family neighbourhood and their children (now adults) are all free from goitre.

reason of their environment. Yet the influence of intermarriage among goitrous persons living in an endemic area is also quoted as giving rise to the hereditary transmission of goitre or to its predisposition. Intermarriage undoubtedly occurs frequently in areas of endemic goitre because they tend to be remote or mountainous and often difficult of access. Joll (1932) mentioned this and stated that the existence of a hereditary transmission of goitre was favoured by the higher percentage of goitrous children born in endemic areas to parents who were born goitrous than to those of whom only one was affected. He added that, when goitrous parents migrated from endemic areas, the children born subsequently might be free from the disease and that the goitrous tendency disappeared in the course of one or two generations. Brain (1926) also rejected the assumption that environmental factors could alone explain the familial occurrence of simple goitre, because some families in endemic areas were disproportionately affected, because members born and brought up in non-endemic areas might also develop goitres, and because hereditary goitre was known to occur sporadically in non-endemic areas. He therefore postulated an inherited predisposition in the form of a defective utilization of iodine as an aetiological factor in some cases of simple goitre. Gardiner-Hill (1934) supported this hypothesis by recording a family affected by endemic goitre in which the emigration of several

female members to non-endemic areas on marriage did not prevent the subsequent development of goitres in themselves and in two of their children who were born later. Murray and Wilson (1945) have also suggested that the same inherited defect in iodine utilization may exist in cases of deaf-mutism which tend to occur in areas of England where the iodine-content of the water is low and endemic goitre or cretinism co-exist. There is thus a certain amount of evidence suggesting the presence of a hereditary factor in the occurrence of simple goitre, but its demonstration beyond doubt would be a formidable task in the presence of such a powerful environmental influence as iodine deficiency.

The family tree from a patient in the present series with a non-toxic goitre illustrates the difficulty in attributing a role to heredity as well as to iodine deficiency (Fig. 1).

The genetical evidence from the present study does not indicate any inherited trait in nodular goitre, but it does not, by virtue of its limited scope, exclude the possibility, and indeed this cannot be ignored. The concept of an inherited defect of iodine utilization resembles in some respects the long-suggested theory of inherited 'thyroid weakness' which was invoked to explain a variety of thyroid diseases and is discussed below in relation to exophthalmic goitre.

Factors in the Familial Occurrence of Exophthalmic Goitre

Exophthalmic goitre, in contradistinction to simple and nodular goitre, is not associated with a dietary deficiency of iodine and does not occur with undue frequency in any particular areas. A familial occurrence of the disease has never been successfully explained by the inheritance of a Mendelian dominant or recessive characteristic for the disease itself, and some authorities have fallen back upon the hypothesis of an inherited 'thyroid weakness' or 'defective thyroid stock'. This has been described in terms of a general defect of the thyroid gland and not as a predisposition to exophthalmic goitre in particular. Thus the sponsors of the hypothesis have been at pains to record families in which toxic goitre, simple goitre, nodular goitre, myxoedema, or cretinism have occurred in the same or succeeding generations. Souques and Lermoyez (1919) postulated 'une fragilité thyroidienne rendant le corps thyroide plus accessible, plus sensible aux diverses infections et intoxications' while Vallery-Radot (1922) and Rundle (1941), who were unable to demonstrate any Mendelian transmission of thyroid diseases, believed in a hereditary thyroid weakness which manifested itself by different thyroid disorders. Such an indefinite hypothesis as 'thyroid weakness' only begs the question as to whether exophthalmic goitre itself is inherited, and it can be criticized on several grounds. Firstly, families containing members affected by several thyroid disorders are not common and the diseases can often be explained by the presence of environmental factors which favour the development of simple goitre and its not infrequent sequels of nodular goitre and secondary thyrotoxicosis. One notable family in the

present series included examples of exophthalmic goitre, retrosternal goitre, toxic goitre, disseminated sclerosis, myxoedema and pernicious anaemia, and bronchiectasis (Fig. 2). Such families are certainly not common enough to justify any generalizations.

A second major criticism of the 'thyroid weakness' theory is that cases of thyrotoxicosis in recorded family trees have not been separated into exophthalmic goitre (primary thyrotoxicosis) and secondary thyrotoxicosis. These two varieties of the disease differ significantly, and by definition, in

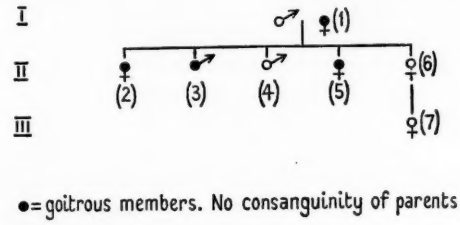

FIG. 2. (1) Died of toxic goitre.
(2) Retrosternal goitre removed at operation.
(3) Died of thyrotoxic heart failure.
(4) Died of disseminated sclerosis.
(5) Died after thyroidectomy for exophthalmic goitre.
(6) Has myxoedema and pernicious anaemia.
(7) Has bronchiectasis.

that exophthalmic goitre occurs in previously non-goitrous individuals, whereas secondary thyrotoxicosis supervenes in persons already possessed of a simple goitre which with the passage of time has usually become nodular. This cardinal difference at once confuses any questions of inheritance when both types are taken together, because simple goitre, as has already been suggested, can mainly be accounted for by environment or individual factors, while no such factors are known to exist in exophthalmic goitre, in which, however, there is evidence in favour of an inherited liability. Thus to include both types of goitre and attribute them to heredity, 'thyroid weakness', or any common cause is to invite erroneous conclusions.

The results of the present study have, in fact, gone far to show that there is little tendency for the relatives of patients with exophthalmic goitre to be affected by simple goitre, and conversely that patients with nodular goitre, the outcome of simple goitre, have very few relatives with exophthalmic goitre. That patients and their affected relatives should thus tend to have the same type of goitre is not only in favour of different causal factors in each type, but also is against any general thyroid weakness which should manifest itself by a wider variety of thyroid disorders. Furthermore, exophthalmic goitre is no longer to be regarded as a purely thyroid defect, but as a syndrome or mosaic of symptoms whose ultimate cause may well reside outside the thyroid gland. For these reasons, therefore, the hypothesis of an inherited thyroid weakness can be rejected as a factor in the production of exophthalmic goitre.

The Inherited Liability to Exophthalmic Goitre

The present study has confirmed a familial occurrence of exophthalmic goitre and the genetical evidence points to the inheritance of a recessive characteristic which confers a liability to develop the disease and is, perhaps, necessary for its occurrence. Consideration of the nature and clinical recognition of this inherited liability lies beyond the scope of the present paper, and indeed the matter is largely conjectural, but a brief suggestion is permissible. It is possible that the inherited liability to exophthalmic goitre may be a personality-type characterized by a constitutional nervous instability affecting particularly the autonomic nervous system. This was suggested by Warthin (1928) in association with hyperplasia of the thymus and lymphoid tissues, while Eason (1927) believed that it occurred in persons of particular bodily builds, but general experience does not bear out the occurrence of exophthalmic goitre in persons with any particular anatomical constants. Moschcowitz (1930) stressed an inherited constitutional nervous instability in persons suffering from exophthalmic goitre, although he gave no genetical details. He believed that it might remain latent so that all those members of a family who possessed it need not necessarily develop exophthalmic goitre, although they might have various nervous manifestations. With some other additional exciting factor, however, such as psychic trauma, infection, or sex-epoch, florid exophthalmic goitre could develop. More recently Moschcowitz and Bernstein (1944) have identified this constitutional nervous instability with neurocirculatory asthenia, but this cannot be unreservedly accepted. However, the recessive characteristic detected in the present study, which confers a liability to exophthalmic goitre, might be the same as that suggested by Moschcowitz and the possibility merits further investigation. Halliday (1943) has recently drawn attention to the psychosomatic affections, of which exophthalmic goitre is one, and future studies of the disease must include a more extended inquiry into the underlying personality and constitution of those affected by it.

Summary

1. The familial or hereditary occurrence of goitre has been investigated in 90 cases of exophthalmic goitre and 111 cases of nodular goitre.

2. The goitrous relatives of patients with exophthalmic goitre were predominantly affected by exophthalmic goitre.

3. The goitrous relatives of patients with nodular goitre were almost exclusively affected by simple or nondescript goitre.

4. Genetical evidence strongly suggests the inheritance of a recessive factor favourable to the occurrence of exophthalmic goitre.

5. There is no evidence from this study of an inherited trait in nodular goitre, but the possibility of it cannot be ignored.

6. It is suggested that the inherited recessive factor in exophthalmic goitre may prove to be a personality-type or a constitutional nervous instability.

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ADDENDUM

An important monograph entitled *Heredity in Graves' Disease* (E. Bartels, Copenhagen, 1941) recently became available, but could not be commented upon in the text of our paper. The author's material comprised 197 cases of Graves's disease and 'toxic adenoma' of the thyroid (toxic nodular goitre) from Copenhagen. Consanguineous marriage in parents was recorded once. In 69 cases only was the diagnosis definitely Graves's disease, and a family history of goitre was noted in 42 per cent. of these. Bartels detected a recessive characteristic for inheritance of Graves's disease which was partially sex-limited to women with a manifestation in them of 70 to 80 per cent. In respect of Graves's disease, therefore, the results of our study corroborate Bartels's findings. We feel, however, that the evidence for recessive inheritance has been obscured by the inclusion of a large number of nodular goitre patients both among the relatives and the propositi. It is of interest to note that the occurrence of Graves's disease and goitre among the female population of Copenhagen was estimated at 0·4 and 1·1 per cent. respectively.

THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1945

THIRTY-NINTH ANNUAL GENERAL MEETING

THE THIRTY-NINTH ANNUAL GENERAL MEETING was held in London on Friday and Saturday, 13 and 14 April 1945, at the London School of Hygiene and Tropical Medicine. The attendance book was signed by 112 members and 24 visitors. The proceedings began at 10.5 a.m.

The President, Major-General Sir Henry Tidy, was in the Chair.

The Minutes of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

The Deaths of the following Honorary Members were reported by the President with regret. Sir Arthur Hurst, who had been nominated for the Presidency in 1944, but had not held Office, as the Annual General Meeting had been cancelled; Professor J. Lewellys Barker, Dr. Judson Bury, and Lord Dawson of Penn, also of Dr. Uvedale Owen, the first member of the Association to die on service in the present war.

The Annual Accounts were presented by the Treasurer, who pointed out that the Association has about £1,000 capital, mainly because the expenses of Meetings have been less as a result of cancellation. The Treasurer explained the relationship between the Association and the *Quarterly Journal of Medicine*, and referred to the recent criticisms of the *Journal* and the discussions between the Executive Committee and the Editors. The Treasurer hoped that it would not be found necessary to raise the Subscription of the Association. The meeting approved the adoption of the Annual Accounts.

Quarterly Journal of Medicine. Sir Francis Fraser welcomed the comments of the Treasurer. He gave reasons for the exiguousness of the *Journal* during the war, and stressed the amount of work which the Editors have to do in the preparation of papers. He appealed to Members to encourage and assist their younger colleagues in the preparation of papers for the *Journal*. The President expressed the thanks of the Association to the Editors, and felt sure that with the help of the Members, and improvements in circumstances, misgivings about the *Journal* would disappear.

Admission of Women to Membership of the Association. The Secretary proposed and Dr. A. V. Neale seconded, that in Rule 2 the word 'men' should be taken to imply also 'women'. This was approved.

Number of Extra-Ordinary Members. It was agreed that next year the Executive Committee should be allowed discretion to increase the number of nominations to the Extra-Ordinary Membership, in view of the possible need for an increase in the number of places for ordinary Membership for men returning from the Services.

Election of Officers. Dr. Gordon M. Holmes was elected President. On taking the Chair, he expressed his appreciation of the honour, and the thanks of the Association to Sir Henry Tidy for his outstanding services to the Association.

Election of Executive Committee

President: Dr. Gordon M. Holmes.

Treasurer: Professor L. J. Witts.

Secretary: Dr. C. E. Newman.

Members for England:

Sir Adolphe Abrahams.
Dr. T. Izod Bennett.
Dr. R. C. Clarke.
Dr. L. B. Cole.
Professor J. C. Spence.
Dr. C. P. Symonds.

Members for Scotland:

Dr. J. Craig.
Professor G. B. Fleming.
Dr. A. Rae Gilchrist.

Members for Ireland:

Dr. R. S. Allison.
Dr. G. C. Dockeray.
Dr. P. T. O'Farrell.

Election of Extra-Ordinary Members

Dr. J. Murray Bligh.
Dr. T. F. Cotton.
Professor G. B. Fleming.
Dr. Donald Hall.
Dr. A. Fergus Hewat.
Professor A. M. Kennedy.
Dr. A. R. Parsons.
Professor K. D. Wilkinson.

Election of New Members

Cyril George Barnes, M.D., F.R.C.P., Assistant Director of the Medical Unit, St. Mary's Hospital.
Donald Marcus Fielding Batty, M.B., F.R.C.P. (Ed.), Late Lecturer in Therapeutics, Edinburgh University.
Leslie John Davis, M.D., F.R.C.P. (Ed.), Senior Lecturer, Department of Medicine, Edinburgh University.
Findlay James Ford, M.D., F.R.F.P.S., Senior Assistant to Professor of Pediatrics, Glasgow University.
Percy Ellis Thompson Hancock, M.B., F.R.C.P., Assistant Physician, Royal Free Hospital.
Evan Jones, M.D., F.R.C.P., Assistant Physician, St. Thomas's Hospital.
Lawrence David Wellwood Scott, M.D., M.R.C.P., Assistant to the Regius Professor of Medicine, Glasgow.
William Carey Smallwood, M.B., M.R.C.P., Assistant Physician, Birmingham United Hospital.
Alan Thompson, M.D., F.R.C.P.(I.), Honorary Physician, Richmond Hospital, Dublin.
Richard Robertson Trail, M.B., F.R.C.P., Physician, Royal Chest Hospital.

SCIENTIFIC BUSINESS

Friday Morning

Dr. Sheila P. V. Sherlock (introduced by Dr. J. McMichael) spoke on *Jaundice in Heart Failure*. A case of jaundice developing during the course of congestive heart failure was described. Two aspiration liver biopsies showed a progressive centri-lobular or cardiac cirrhosis, and also evidence of stasis of bile in the liver lobules. These findings were confirmed by autopsy. The pressure in the right auricle was 36 cm. of water. It was calculated that the venous pressure existing in the hepatic sinusoids was greater than that at which bile can escape from the liver. The external pressure against the liver-cell column thus produced a mechanical blockage of the bile canaliculi.

In reply to comments by Surgeon Rear-Admiral J. W. McNee, Drs. East, William Evans, and Professor K. D. Wilkinson, Dr. Sherlock said that jaundice, with manifestations of an obstructive cause, was common in congestive heart failure.

DR. C. HARDWICK described *The Influence of High and Low Protein Diet on the Duration of Infective Hepatitis.* In a carefully controlled experiment at a Royal Air Force Hospital, alternate cases of infective hepatitis were given a diet of 180 gm. of protein and 50 gm. of protein. The caloric value and vitamin content of each diet was the same. Of 76 patients, 41 received the high, and 35 the low protein diet. The series were similar in severity. The duration of biliuria, hyperbilirubinaemia, and treatment were, in the high protein series 8, 17·7, and 19·3 days respectively, and in the low protein series 9·5, 18·4, and 20·9 days. These two series of figures show no statistical difference.

DR. PARKES WEBER said that he had noticed that young foreigners coming to England eat meat to excess and tend to contract jaundice. DR. IZOD BENNETT suggested that the fat in the meat might have an influence. PROFESSOR WITTS stressed the importance of negative results, such as Dr. Hardwick's, in combating erroneous notions. PROFESSOR DAVIDSON suggested that low protein diets might be dangerous in chronic disease of the liver. PROFESSOR PETERS thought that the right mixture of amino acids might still be found useful. DRS. CLIFFORD WILSON, PATTERSON, and BYWATERS also contributed to the discussion.

DR. PARKES WEBER described *The Non-ocular Features of Sjögren's Syndrome.* Sjögren of Stockholm had established the syndrome which included kerato-conjunctivitis sicca, xerostomia, rhinitis sicca, pharyngitis sicca, and laryngitis sicca. DR. PARKES WEBER had seen in such cases various other features such as the Plummer-Vinson syndrome, achlorhydria, dryness of the skin, atrophic changes in the vagina, alopecia, accelerated erythrocyte sedimentation, hypochromic anaemia, low blood-pressure, low blood-sugar, and low blood calcium, Raynaud-like blueness of hands and feet, telangiectases on lips and tips of fingers, telangiectatic, pigmentary and scleroderma-like changes in the legs, delusions, and epileptic fits. He discussed the differential diagnosis and suggested that, although the aetiology was unknown, it was possibly connected with derangement of the vegetative nervous system.

SIR HENRY TIDY and DR. PEARSON spoke on the associated swelling of the salivary glands.

DR. G. L. W. BONNEY (introduced by PROFESSOR G. W. PICKERING) spoke on *Gastric Pain.* After a short review of the theories of Palmer, Hurst, Ryle, and Hardy on the stimulus to gastric pain, he gave observations on a series of 54 patients with gastro-duodenal ulceration. Gastric acidity was measured throughout by the quinhydrone electrode. In all of 21 patients spontaneous pain was associated with high gastric acidity, and in 27 of 34 patients ingestion of hydrochloric acid reproduced pain while the ulcer was active. No change in intragastric tension could be observed, and examination of the stomach by X-rays during pain showed reduction of tone and peristaltic activity. It was concluded that rise of hydrogen-ion concentration furnished the ordinary stimulus to pain, which was not dependent on any rise of gastric tension or activity.

DR. HARDY recalled that Wolf and Wolff had found that the mucous membrane, which is altered when an ulcer is present, was sensitive to thermal, chemical, and mechanical stimuli. DR. AVERY JONES suggested that in the presence of superficial lesions, acid may seep into the muscularis mucosae and cause pain just as acidification of muscle elsewhere is painful. DR. IZOD BENNETT felt that as hydrochloric acid closes, rather than opens, the pylorus, it was still not clear that hypertonus was not the cause of pain. SIR ADOLPHE ABRAHAMS pointed out that pain is associated with partial filling, not with fullness and emptiness of the stomach. DR. COOKE recalled that solid potassium bromide causes pain. PROFESSOR RYLE agreed that acid produced pain, but asked how it did so. Pain may afflict people without ulcers and without gastric acidity. He suggested that the states of the cardia and pylorus must be significant. DR. L. D. W. SCOTT instanced the difficulty presented by cases which we know have an ulcer, because they have perforated, and yet have had no pain. SIR HENRY TIDY said that he had been gratified by the return to the teaching of his student days presented by the communication, but that the audience seemed now to be upsetting it all again. He suggested that multiple factors must be concerned, and not acidity alone. DR. PEARSON thought that adhesions to neighbouring structures might be a contributory factor. PROFESSOR PICKERING replied to the speakers. He thought the pain caused by solid potassium bromide was a simple reaction to injury. There was no real evidence as to whether pain originated in the ulcer itself, or in the mucosa; gastroscopic studies on this point

were needed. Achlorhydric patients may produce acid at times, so that a test meal is not a sure guide. The threshold for painful stimulation by acid seems to vary from patient to patient. Sodium hydroxide causes pain if sufficient is given, and this suggests that pain has a chemical basis. There is no direct evidence that peristalsis or tension caused pain; it is true that vigorous contractions produce hunger pain, but this is different from the pain of an ulcer.

The Meeting adjourned to Luncheon at the Holborn Restaurant.

Friday Afternoon

DR. H. COOKSON communicated some *Observations on Thiouracil in Goitre.* The action of thiouracil in 52 patients with goitre was studied over a period of 18 months, the primary purpose being to determine its effects on the toxic symptoms of goitre. In 26 cases with unquestionably raised metabolism the drug reduced this to normal and relieved symptoms. In 16 cases with mild or doubtful toxicity the effects were not so clear cut, and there were some apparent failures. In 10 cases of doubtful toxicity there was no effect on the metabolic rate. Symptoms of hypothyroidism could not be produced. Observations on blood-cholesterol and auricular fibrillation were reported. No serious toxic reaction to the drug had occurred. The place of thiouracil as an alternative and as a supplement to thyroidectomy in the treatment of toxic goitre was discussed.

DR. JENNER HOSKIN upheld thyroidectomy. DR. NATTRASS, on the other hand, favoured thiouracil. DR. S. L. SIMPSON agreed with DR. HOSKIN that surgery still had a place in treatment, but thought thiouracil a good possible alternative to surgery or radiotherapy. DR. LESCHER and DR. MORLOCK spoke of their experience, and DR. L. D. W. SCOTT said that in some cases the drug had no effect on the histological appearances of the thyroid. PROFESSOR DAVIDSON said that after six months on a maintainance dose of 0·1 gm. daily, or on alternate days, it seemed that even after stopping the drug the patients do not relapse. PROFESSOR WILKINSON thought that surgery offered a quick and certain result, and as there had been no trouble with the last 100 of his thyroidectomies he wondered whether surgery was not the better treatment. DR. COOKSON, replying, held that thiouracil, although still in the experimental stage, was a great advance in therapeutics, though it might never displace surgery completely. There is little need to be worried by the possibility of toxic effects.

DR. A. HUNTER (introduced by DR. J. PARKINSON) discussed *Cardiac Enlargement in Chronic Anaemia.* Cardiac size had been studied by the superimposition of comparable teleradiograms taken at various stages of treatment in 33 mixed cases of anaemia of moderate or considerable severity. Enlargement was present in 14, doubtful in six, and absent in 16. Cardiac size decreased after treatment in 11 cases, becoming normal in eight. Enlargement was unaffected by treatment in two cases. No correlation could be established between the presence of enlargement and age, or of type or severity of the anaemia, though duration might have been important. The cardiac enlargement diminished with the improvement of the blood occurring early in treatment, even though there was still anaemia. Further improvement in the blood was seldom accompanied by further cardiac diminution. The enlargement was therefore thought to be caused by circulatory disorder, rather than by impaired myocardial nutrition.

DR. E. P. SHARPEY-SCHAFER communicated his findings in regard to *Transfusion and the Anaemic Heart.* In severe anaemia the blood-volume is reduced, and the right auricular pressure, cardiac output, and percentage utilization of available arterial oxygen are increased. Transfusion raises the right auricular pressure, and in normal subjects increases cardiac output, but in severe anaemia, cardiac output may fall. Acute pulmonary oedema follows in some cases, and the blood-pressure may rise. He suggested that this falling cardiac output is similar to Starling's overloaded heart-lung preparation, where increased venous filling-pressure results in a falling cardiac output. The objective of transfusion in severe anaemia is long-term benefit from increased arterial oxygen content, while venous filling-pressure is raised as little as possible. Hence the small, slow, concentrated transfusion. Among other suggestions, he included the use of the propped-up 'cardiac' position, and clinical observations of the venous pressure.

These two communications were discussed by DRS. MORGAN, JONES, and LANGLEY, PROFESSOR WILKINSON, DRS. HILTON, MCMICHAEL, C. WILSON, WHITTLE, PATTERSON, and WILLIAM EVANS.

PROFESSOR L. S. P. DAVIDSON described the *Use of Proteolysed Liver in the Treatment of Refractory Megaloblastic Anaemia.* During the past four years he had treated 269 cases of macrocytic anaemia. After the exclusion of 41 cases with normoblastic marrows and 175 classical cases of pernicious anaemia, there remained 52 cases: steatorrhoea, 19; pernicious anaemia of pregnancy, 24; idiopathic megaloblastic anaemia, 9; and of these, about half the cases in the first two groups, and all the cases in the third group were refractory to parenteral liver therapy. Fourteen consecutive cases were treated with proteolysed liver, with dramatic results in 13. It can be assumed that certain cases of megaloblastic anaemia are deficient in some factor in addition to the anti-anaemic principle in liver, and that this factor is removed or destroyed during the preparation of parenteral liver extracts.

The meeting adjourned to tea at the London University Club at 4 p.m.

DR. F. AVERY JONES discussed *The Aetiology and Mortality of Gastroduodenal Haemorrhage.* He presented an analysis of 400 consecutive personal cases of haematemesis and/or malaena treated by liberal feeding and transfusion. One-third of the cases showed no X-ray evidence of peptic ulcer and no other cause was manifest from the history or examination. Early gastroscopy showed rapidly healing gastric ulcers in one-third of this group. Twenty-nine per cent. of the cases were over 60 years of age. The mortality for the whole series was 8·5 per cent.; that for peptic ulcer patients only 6·75 per cent. Two-thirds of all the fatal cases from peptic ulcer had an associated serious complication on admission, such as pneumonia, acute perforation, generalized oedema, or senility. Very few could have been saved by surgery, but it was worth considering for recurrent brisk haemorrhage from chronic gastric ulcer when the patient was over 50 years of age.

DR. ALICE STEWART, DR. F. J. KEMP, and MR. R. G. MACBETH (introduced by PROFESSOR WITTS) described a technique for demonstrating *Oesophageal Varices* during a barium swallow, and showed a number of X-rays of typical cases. In a series of 14 cases of cirrhosis and four of splenic anaemia, varices were present in seven of the former and in three of the latter. The incidence was higher in the cases of advanced cirrhosis than it was in the early cases, and only one case showing varices had not had a haematemesis. None of the cases in which varices were not visible in the X-ray film had had a haematemesis. Two cases with recurrent haematemeses were treated by direct injection of the varices with 1 per cent. sodium morrhuate solution. One to three varices were injected at a time, and the operation was repeated at weekly intervals. In one case the bleeding recurred a month later, but in the other there had been no recurrence of bleeding for over a year, and re-examination 12 months after the operation showed that the varices were diminished in size and number.

SIR HENRY TIDY and PROFESSOR DAVIDSON commented on these two communications. MR. MACBETH demonstrated the injection instrument.

DR. R. MORTON GILL described *The Effects of Administration of Intestinal Mucosa in Ulcerative Colitis.* Acting on the theory that some of these cases might be due to a deficiency produced in or by the intestine, experiments were made on feeding a patient on pig's small intestine (raw). Remissions were regularly induced and maintained, and relapses always followed when the treatment was stopped. This was continued over several years. Similar results have been obtained in other cases, and in yet others no response has been obtained. A dried, powdered preparation is also effective by mouth, but the dried material has to be properly prepared. There is evidence that the results are neither coincidental or psychological. In reply to a question by DR. LIVINGSTONE, DR. MORTON GILL said that half a pound of raw small intestinal mucosa, or one ounce of the dried powder per diem was a sufficient dose.

It was possible this year to hold again the *Annual Dinner,* and 65 members and their guests accordingly dined at the Holborn Restaurant, with the PRESIDENT, DR. GORDON M. HOLMES, in the Chair.

Saturday Morning

A Discussion was held on *Primary Pulmonary Tuberculosis in Young Adults.*

AIR COMMODORE R. R. TRAIL, introducing the subject, said that the theory still generally held is that pulmonary tuberculosis is of two types, primary and post-primary. No intermediate form is visualized. The second is considered to be due to the first, except in rare cases of fresh exogenous infection, and yet to appear in an area

entirely dissociated from that of the first lymphatic deposit. It is probable that primary infection at any age produces many pin-point lymphatic foci, with or without a larger node recognizable by X-rays or post-mortem examination. The fleeting areas of loss of translucency in primary adolescent disease represent lymphangitis round these foci. Findings by Mass Radiography over the past four years in the Royal Air Force suggest the following empirical theories: (1) That adult phthisis may be the third of three phases of tuberculosis in man, all three following the initial infection, and each commencing as lymphangitis. The first appears round the initial foci, the second round the posterior apical bronchus, and the third round one of the remaining posterior bronchi of the upper or lower lobe. (2) There may be two types of adult phthisis, the first a reawakening of an apparently calcified primary childhood infection, the second a continuing primary infection contracted in later life. (3) That primary infection after childhood, which leads to lung lesions, is not necessarily a dangerous process. It is probable that in a majority of two to one it goes rapidly and without clinical illness to a quiescent tertiary stage, showing marked tendency to natural healing.

Dr. F. Ridehalgh said that, known contact being absent, 7·5 per cent. of Londoners, aged 15 to 30 years, are tuberculin-negative. Nurses entering London training schools at the age of 17 years show 26 per cent., at 30 or more 9 per cent. of negative reactors, whether they come from urban or rural environments. Nurses from rural Ireland or Wales show 34 per cent. of negative reactors at ages 15 to 30 years (Prophit survey). Radnorshire school children at the age of 15 years show 84 per cent. of negative reactors to the tuberculin patch test (Jones Davies). Exposure of negative reactors to open cases of tuberculosis will produce 78 per cent. of primary infection within a year, 95 per cent. within three years. Primary infection of nurses in general hospitals leads to pulmonary tuberculosis at the rate of 26 cases per 1,000 per annum. Nurses initially tuberculin positive develop only 7·5 cases per 1,000 per annum. The types of lesions are the same in both groups, thus primary infection in young adults carries a definite risk, but since, even so, the majority of nurses acquiring primary infection escape disease, it seems that factors of resistance exist which are not yet defined. These may be inherent in the reticulo-endothelial system. Migration from rural to urban areas may increase the tuberculosis morbidity as a result of primary infection. No evidence of a special racial liability was found in the Prophit survey. There is an urgent need for a large-scale trial of methods of immunization of Mantoux-negative persons exposed to infection.

Dr. Izod Bennett said that in a series of 35 cases of erythema nodosum in young women between the ages of 17 and 24 years, tubercle bacilli had been recovered by gastric lavage in 26. None of these 26 had any symptoms of lung disease, but lesions were demonstrated by radiography in 14. Of the nine cases in which tubercle bacilli were not found, five had radiological lesions. In all but two cases the course was benign; one of the 14 with both bacteriological and radiological evidence developed a pleural effusion, and one of those negative both bacteriologically and radiologically developed first an effusion and later Pott's disease.

Dr. R. E. Smith had seen six or seven cases of tuberculosis in 600 boys at Rugby between 1931 and 1945. He had found that erythema nodosum was the most common manifestation of primary tuberculosis. In only one case had he found a pulmonary lesion. He thought that nutrition was the most important means of prevention.

Dr. Margaret Macpherson said that there are differences between primary tuberculosis in children and in adolescents or adults. It is more common in children, and unaccompanied, as a rule, by clinical evidence. In young adults, on the other hand, there seems to be a higher rate of clinical abnormality. The primary complex in children, especially in infants, tends to show a greater reaction in the hilar glands than in the lung parenchyma, and it is the hilar adenitis which tends to produce clinical manifestations, by pressure or erosion. By comparison, the glandular enlargements in young adults are less spectacular, and the primary lesion in the lung may rapidly lead to radiological changes of typical tuberculous infiltration. Slides and X-ray film were shown to illustrate these points.

The discussion was suspended while three distinguished French visitors, Professor Lemaire, Dr. Ravina, and Dr. Armand Delisle were admitted and welcomed by the President.

AIR COMMODORE TRAIL at this point demonstrated some films showing lymphangitic spread of tuberculosis.

DR. WHITTLE wondered what the relation was between haematogenous infection and the development of immunity and infections appearing later, and instanced the case of a child operated on for a hernia, in the sac of which tuberculous peritonitis was found.

SIR ADOLPHE ABRAHAMS referred to the rarity of tuberculosis in athletes.

PROFESSOR WITTS asked what one should do in practice. A nurse or a student is found to have a suspicious radiological appearance, or is suspected to have tuberculosis after an influenza-like illness. Ought one to conduct an exhaustive search for tubercle bacilli? Otherwise how is one to know whether the disease is tuberculous? He suggested that a discussion such as this should help in making practical decisions.

PROFESSOR J. C. SPENCE pointed out that infection in childhood may be dangerous. It is true that between the ages of 2 and 5 years primary tuberculosis is relatively benign, but it is very dangerous in the first six months of life, and in adolescence, between the ages of 12 and 15 years. He suggested that in practice it is wise to remove the patient from further contact, but that to put the patient to bed is unphysiological, and asked what other members advised.

PROFESSOR WITTS pointed out that to remove a student from further contact meant shattering his career.

PROFESSOR SPENCE said that he meant, rather, removing the patient from contact with one single person who was the source of danger.

SIR EDMUND SPRIGGS suggested the possibility of really drastic measures. We had eliminated leprosy by isolation, ought not the profession to lift its voice and do something to stop open cases of tuberculosis from spreading the disease? We make a cliff safe by putting a fence on the top, not by providing an ambulance at the bottom. We ought to see to it that the House of Commons understands the prevalence of open tuberculosis in men and in cattle. In the United States less than one-half per cent. of the cattle are tuberculous, all tuberculous reactors among cattle are killed, and farmers are put in gaol for attempting to sell them.

DR. MONCRIEFF asked whether SIR EDMUND SPRIGGS would segregate a young adult without symptoms, in whose gastric contents tubercle bacilli had been found.

PROFESSOR DAVIDSON remarked that there are three general practitioners in Edinburgh going about their business with open tuberculosis.

DR. LIVINGSTONE pointed out that primary tuberculosis in students and nurses does progress directly to the adult type of disease. He suggested that each case should be treated on its merits, that the recently Mantoux-positive should have two or three months' convalescence, and should then be allowed to go on with his work under close observation. The period of danger was the 15 to 24 months after primary infection. He observed that in 1,000 cases investigated erythema nodosum had been found to be a very rare manifestation.

DR. ARMAND DELISLE said that B.C.G. confers at any rate a partial immunity, though infection is still possible from continued contact. Scarification is the most effective method. Every child, he thought, should be immunized with B.C.G.

DR. MONCRIEFF asked some practical questions. Is the three months' convalescence recommended to be at the public expense? Is the case to be notified, and is it to be treated in a sanatorium or sent to a convalescent home?

DR. IZOD BENNETT confessed that he for one was mystified as to what was to be done with cases sent to sanatoria by administrative officials.

DR. MORLOCK suggested that if all contact with tuberculosis were eliminated, the population would become completely susceptible, and when a case was introduced from abroad, we would be in a state resembling that of the South Sea Islands on the introduction of a completely new disease.

SIR EDMUND SPRIGGS doubted the soundness of the South Sea analogy, because the absence of tuberculosis among cattle in the United States seemed to falsify it. He

said that the London County Council was classifying its sanatoria according to the different stages of tuberculosis.

Dr. George Graham felt that sanatoria must be classified, and convalescent cases sent to the appropriate ones.

Air Commodore Trail, replying, remarked that he had seen five cases of tuberculosis in Rugby Internationals in one year. New methods of culture are finding increasingly more positive sputa. In England a case of open tuberculosis can refuse to be treated; in Canada such a person would be sent to prison. In time we shall adopt drastic steps in dealing with this problem. A patient with tuberculosis, it must be remembered, does not necessarily go about infecting other people. In 21 years' experience children at Papworth have not become infected. Preventoria are wanted as well as sanatoria, and 'intimation registers' as well as tuberculosis registers. Finally, it must not be forgotten that patients from X-ray units too often end up in the hands of the psychiatrist.

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